BUREAU OF HYGIENE AND TROPICAL DISEASES.

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SLEEPING SICKNESS.

ECONOMIC ADVISORY COUNCIL. **East Africa Sub-Committee of the Tsetse Fly Committee** [HEMMING (Francis), Chairman]. **Report.** Cmd. 4951.—56 pp. 1935. London: H.M.S.O. [1s.]

In May, 1934, the Secretary of State for the Colonies communicated to the Economic Advisory Council the report of the Conference on Tsetse and Trypanosomiasis Research held at Entebbe in 1933, and also the conclusions of the recent Governors' Conference on the same subject, and asked that he might be furnished with the observations of the Council's Tsetse Fly Committee on these papers. On 3rd July, 1934, the Earl of Plymouth, Chairman of the Tsetse Fly Committee, appointed an East Africa Sub-Committee of that Committee to prepare a report on these questions.*

In the introduction to their Report the Sub-Committee state that one of the most important subjects they have had to consider was the question of the future of the Human Trypanosomiasis Institute, Entebbe. They received valuable assistance in this part of their inquiry from Dr. DUKE and from Dr. KAUNTZE, Director of Medical Services, Uganda. In addition they are much indebted to Dr. Edward MELLANBY, Secretary, Medical Research Council, for the assistance which he gave in regard to the co-operation which might be obtained from the Medical Research Council in carrying out certain investigations suggested by the Conference.

The Sub-Committee state that they found it convenient to preface their discussion with a general outline of the problem as a whole, and consequently in Section II of the Report they describe briefly the main characteristics of trypanosomiasis, both animal and human, and the principal methods available for controlling it. Section III is devoted to a discussion of items of fundamental research, the object of which is to obtain further knowledge of the causes of the disease; and Section IV emphasizes the necessity for maintaining contact between the scientific work on these subjects being carried out in different parts of Africa and the world. Section V consists of a summary of the principal conclusions and recommendations of the Sub-Committee.

* The members of the Sub-Committee were:—
Mr. Francis Hemming, Chairman; Dr. W. Horner Andrews; Sir Arthur Bagshawe; Sir Guy Marshall; Sir Thomas Stanton; Dr. C. M. Wenyon; Mr. F. G. Lee; Mr. D. H. F. Rickett, Secretary.

Section II. The control of trypanosomiasis in man and animals.—After giving an excellent and readily understandable statement of the "General Character of the Problem" the report passes to a consideration of the various available methods of control. These are of three kinds:—

i. *Control by administrative measures.*—Broadly these represent an attempt to prevent or eradicate infection by controlling the movements of population. There seems little doubt that the spread of sleeping sickness has been largely assisted, if not caused, by the development of the means of communication which took place at the end of last century. Obviously infected persons should not be at liberty to migrate where they please, fishing in fly-infested areas should not be permitted except under control, and access to watering places similarly endangered should only be allowed after clearing of the bush. Such measures as these may be regarded as part of the routine to be observed in preventing the spread of infection. Administrative control in the wider sense has, however, a larger scope than this. The policy of controlling population movements has in most cases been designed to play a large part in furnishing a solution of the sleeping sickness problem. The most drastic and most obvious of these measures is the evacuation of the population from an area affected by an outbreak of sleeping sickness. Reference is made to the evacuation in Uganda and the benefit which it was anticipated would accrue therefrom. Subsequent discoveries have shown, however, that there is little prospect of success for such a policy, if unaccompanied by direct attempts to exterminate the fly. Experience has shown that temporary withdrawals of the population would often in practice tend to become permanent. Apart from the grave effects upon the industry of the areas concerned, the absence of population promotes the growth of bush and multiplication and spread of game; and usually these factors operate together to assist the advance of fly. Undoubtedly the most effective means of preventing the spread of fly is by the concentration into closer settlements of scattered native populations. It has been found that a settlement with a minimum population of 3,500 to 4,000 is large enough to secure freedom from fly roughly two years from its establishment. The Entebbe Conference considered this method of control very carefully and agreed that organized settlement and development of this nature was ordinarily the most important general preventive measure which could be taken by administrations in the campaign against trypanosomiasis, and this view is fully shared by the Sub-Committee.

ii. *The control of tsetse flies.*—This section of the report is in large measure devoted to an account of the results and progress of the work proceeding in Tanganyika under the direction of Swynnerton. The biggest fly belt in Tanganyika is 500 miles at its longest by 300 miles at its widest point. In order to deal with a problem of this magnitude these great fly belts must be subdivided by means of suitable barriers into a number of small compartments from which the fly cannot escape. At the present time the great Shinyanga fly-belt has been divided up by corridor clearings into a number of blocks in which different methods of eradicating tsetse are being tested, *e.g.* (1) organized grass fires, (2) differential, as opposed to wholesale, clearing, (3) fly and game barriers formed by dense strips of thicket, (4) fly traps, and (5) eradication of the fly by protecting blocks of bush from grass fires. The advantages and limitations of these various measures are discussed in some detail.

iii. *The control of trypanosomiasis by chemotherapy.*—The third of the principal methods of control is the treatment of the disease by drugs. It has been shown by a number of clinical trials that " Bayer 205 " has a definite prophylactic value, but the sub-committee agree with the Entebbe Conference that further information is required before the drug can be employed to the fullest effect in this direction. There is little doubt that " Bayer 205 " remains in the blood and tissues for a considerable time, probably for several months, and that it is eliminated in the urine very slowly. Very little work has, however, been done on the rapidity or manner of excretion of the drug from the animal body. The Entebbe Conference recommended " that the Medical Research Council should be approached with a request to work on this problem " and they suggested that the subject might be of interest to Dr. WORMALL, who is engaged on cognate research under the auspices of the Medical Research Council, In order to give consideration to this suggestion, the sub-committee invited the Secretary of the Medical Research Council to attend one of its meetings and discuss the matter with them. Dr. MELLANBY informed the sub-committee that Dr. WORMALL had expressed his willingness to undertake preliminary investigations on the problem in question. WORMALL proposed to study the methods of STEPPUHN and UTKINA-LYUBOWZEWA (1924) and of LANG (1931) for the chemical determination of " Bayer 205 " and then to examine the excretion of the drug by small animals after one or more injections.

At the same meeting the sub-committee discussed with Dr. MELLANBY the recommendation put forward by the Entebbe Conference that the Medical Research Council should be approached with a view to interesting prominent British research workers in the synthesis of therapeutic compounds for the treatment of trypanosomiasis. The suggestion of the Conference was that such drugs could then be tested in East Africa. From the discussion which the sub-committee had with Dr. DUKE and Dr. KAUNTZE they had gathered that it was the feeling of those engaged in work on trypanosomiasis in British Territories in Africa " that the drugs at present employed . . . are susceptible of improvement." The Conference was accordingly anxious to secure the co-operation of scientific workers in this country in the production for subsequent trial in Africa of new forms of drug for use against trypanosomiasis. Dr. MELLANBY assured the sub-committee that there is no lack of such new compounds awaiting experimental use in Africa. In 1927, the Medical Research Council, with the co-operation of the Department of Scientific and Industrial Research, appointed a Chemotherapy Committee with the main object of investigating drugs having specific action in trypanosomiasis and malaria. For some years before this, the Medical Research Council had already been supporting two groups of workers engaged in research for new trypanocidal drugs, viz., Professor COHEN at Leeds and Professor BROWNING at Glasgow, and Dr. KING and Miss DURHAM at Hampstead. The Chemotherapy Committee began by inviting a number of well-known chemists to prepare a series of new compounds for test on experimental trypanosomiasis lines which had been carefully discussed before. To deal with the new compounds, another Biological Station under the reviewer at the Liverpool School of Tropical Medicine was established by the Medical Research Council in addition to the two already so engaged. [It would be fairer to say that this centre was established, and is mainly financed, by the Liverpool School of Tropical Medicine,

and that it is supported by an annual grant from the Medical Research Council].

Dr. MELLANBY went on to inform the sub-committee that Professor MORGAN of Teddington had prepared a long series of compounds, which had been examined by Professor YORKE, and that five of these compounds had been selected as having maximal activity. Dr. KING of the National Institute for Medical Research had also discovered two arsenicals of novel type of extreme efficacy in trypanosomiasis of mice and rabbits. Dr. MELLANBY further informed the committee that having regard to the fact that there were now seven drugs which had been synthesized by workers under the Chemotherapy Committee known to have considerable trypanocidal activity, the Medical Research Council believed that the time had come when the best opportunities for the clinical trial of these drugs should be made available. The sub-committee considered the subject in the light of this information, and reached the conclusion that the importance of securing the most precise information possible in regard to the use of these new drugs is such that the appointment of a special investigator to undertake this work would be fully justified. They accordingly recommend that the Secretary of State for the Colonies should invite the Medical Research Council to arrange for an investigator to proceed to Africa for the purpose of conducting clinical tests on trypanocidal drugs.

[The Secretary of the Medical Research Council was a little premature when he informed the Sub-Committee that the Chemotherapy Committee has available 7 drugs ripe for testing in the field. As a matter of fact, only one of these compounds—Preparation S.107 of Professor MORGAN—had been sufficiently examined to justify its despatch to Africa for testing in the field on cases of sleeping sickness. The other six compounds have not so far been administered to man, nothing is known about the dosage in which they could be used, and they have not even been prepared in more than minute amounts.]

SECTION III. PROTOZOAL RESEARCH.—This portion of the report summarizes the work which is being done at the Human Trypanosomiasis Institute, Entebbe, and also the investigations which have been conducted in other parts of Africa by CORSON and others during the last few years. All this work is familiar to readers of this *Bulletin*.

SECTION IV. CONTACTS WITH RESEARCH WORKERS IN OTHER COUNTRIES.—The main purpose of the Entebbe Conference was to co-ordinate the tsetse and trypanosomiasis research being done at the present time in East Africa. From their examination of the program of research drawn up by the Conference the sub-committee is convinced that that result has been in large measure attained. This important subject is discussed very fully in the report.

In the sub-committee's opinion, the publication of the *Tropical Diseases Bulletin* goes far towards filling the need for information felt by research workers in trypanosomiasis. In order that workers in the field should be informed of what is going on in different parts of Africa at the earliest possible moment, Sir Arthur BAGSHAWE, Director of the Bureau, informed the sub-committee that he was prepared to arrange for the list of titles of papers awaiting review, which he compiled each week, to be reproduced in cyclostyle and distributed to the Directors of Medical Services at a small charge. The sub-committee believes that this will be of real service to those engaged on trypanosomiasis research in Africa.

SECTION V. SUMMARY OF PRINCIPAL CONCLUSIONS AND RECOMMENDATIONS.—In this very interesting and important section, the sub-committee first of all summarizes its principal conclusions and then lays down certain definite recommendations. It is unfortunately impossible to reproduce the whole of this section here, but the following are the chief recommendations.

i. *Control of trypanosomiasis in man and animals.*

(*a*) *Control by administrative measures.*—This calls for constant co-operation between the large number of departments concerned. Small *ad hoc* bodies might therefore with advantage be set up in the larger territories to secure an adequate machinery for consultation and discussion of problems as they arise. The proposal that a central body should be set up either in Africa or in the United Kingdom to conduct a general investigation into the principles to be adopted in applying administrative methods of control was not received with favour.

(*b*) *Control of tsetse flies.*—It is strongly recommended that the fullest financial support should be given to the Tsetse Research Department in the Tanganyika Territory. As there is a great danger that the Department may lose the services of officers who by training and past experience are exceptionally qualified for their work, it is recommended that the question of granting permanent pensionable status to the officers now working in the Department should receive consideration at the earliest possible moment. It is also recommended that the biological study of tsetse flies in *rhodesiense*, *gambiense* and *brucei* areas should be included in the program of research; and that the biological study of the stomach contents of the tsetse fly should be undertaken by Mr. C. B. SYMES at the Medical Laboratory, Nairobi.

(*c*) *The control of trypanosomiasis by chemotherapy.*—It is recommended that an investigation of the prophylactic value of Bayer 205 should be undertaken, and that the Secretary of State should invite the Medical Research Council to arrange preliminary investigations on the rapidity of the excretion of Bayer 205 to be carried out by Dr. WORMALL.

With the object of testing the new drugs prepared by the Chemotherapy Committee, it is suggested that the Secretary of State should invite the Medical Research Council to arrange for an investigator to proceed to Africa for the purpose of conducting clinical tests on trypanocidal drugs and to arrange for him to be afforded all necessary facilities for his work, including the concentration in some suitable centre of a sufficient number of sleeping sickness cases who could be kept under observation.

It is also recommended that the Secretary of State for Dominion Affairs should ascertain from the Government of Southern Rhodesia whether it would be possible for the Trypanosomiasis Bureau to test the veterinary effects of some new drugs; and from the Government of South Africa whether these tests could also be undertaken at the Veterinary Research Institute, Onderstepoort.

ii. *Protozoological research.*—It is recommended that in order to enable Dr. DUKE to complete his present experiments, the Human Trypanosomiasis Institute, Entebbe, should be maintained on its present basis till the 31st Dec., 1935, when the Institute as such should be closed; and that thereafter the Medical Department in Uganda should undertake such research as its resources permit.

It is recommended that the fullest support should be given to the work of Dr. CORSON at Tinde, and that the investigations on immunity and the relation of trypanosomes now being carried out by Mr. HORNBY at the Veterinary Laboratory, Mpwapwa, should also form part of the program of research.

The sub-committee also makes recommendations regarding other protozoal research.

The report closes with two Appendixes.—The first reprinting the program of tsetse and trypanosomiasis research in East Africa prepared by the Entebbe Conference; and the second giving an account of diagnostic methods in human trypanosomiasis by Sir Arthur BAGSHAWE. *W. Yorke.*

SELWYN-CLARKE (P. S.). **Trypanosomiasis in the Gold Coast (with Special Reference to 1933–34).**—*Gold Coast Rep. Med. Dept. for Year 1933–34.* Appendix IX. pp. 100–107. With 1 map.

This article opens with a general account of the history of trypanosomiasis in the Gold Coast. In a table the author shows that the incidence of recorded cases of sleeping sickness per 10,000 of all cases treated has steadily increased from 3·2 in 1924–25 up to 56·1 in 1933–34. He points out, however, that particular attention has been paid to the subject on the Gold Coast during the last few years, and that consequently the marked increase in the number of cases reported cannot be attributed entirely to the occurrence of localized epidemics.

After discussing briefly the distribution of the disease in the Colony, the author passes to a summary of the work done during the year 1933–34. In April, MCKERNAN examined 300 persons in the hyperendemic area of Mamprusi under mandate, and found the infection rate (judged by examination of gland juice only) to be about 11 per cent. In August and September of the same year Dr. PURCELL carried out a rather more detailed survey over a large area. He found little evidence of the disease in the eastern and central parts of Northern Mamprusi. In the northern part of the district the incidence of persons suspected to be suffering from the disease was 1·5 per cent. The disease was found to be scattered somewhat scantily throughout Southern Mamprusi, except in the Mandated Territory, where it appeared to be hyperendemic. Towards the end of 1933, a temporary field hospital was established at the centre of this hyperendemic area. A general description of the measures taken to deal with the situation follows.

W. Y.

DUPUY. La maladie du sommeil dans les régions soumises à l'action du Fonds Reine Elisabeth pour l'assistance médicale aux indigènes du Congo Belge (Foreami). Rapport pour l'année 1933. [**Sleeping Sickness in the Regions dealt with by the Queen Elizabeth Funds for the Medical Assistance of the Natives of Belgian Congo (Foreami). Report for 1933.**—*Ann. Soc. Belge de Méd. Trop.* 1935. Mar. 31. Vol. 15. No. 1. pp. 39–84.

This lengthy report describes the results of the anti-trypanosomiasis work done with the aid of the Queen Elizabeth Fund during the year 1933 and compares the position during that period with that during the two previous years.

In his preliminary remarks Dupuy defines the conditions under which lumbar puncture is performed; these are :—

(*a*) *Lumbar punctures for diagnosis.*—These are punctures made on new cases recognized by gland puncture and on suspected cases in whom gland puncture was negative.

(*b*) *Lumbar punctures of elimination.*—After treatment consisting of large doses a puncture of 1st elimination is made at the end of the course of treatment. After an ordinary treatment of 12 injections of 2 gm. the 1st puncture of elimination is made 3 months later. If the puncture of 1st elimination revealed changed spinal fluid the patient is put on treatment again, and a puncture of 2nd elimination is performed 3 months after its termination. If this puncture also reveals a changed spinal fluid the patient is considered to be in a chronic condition ; a third course of treatment is given and this in turn is followed by a puncture of 3rd elimination.

(*c*) *Lumbar punctures of control.*—When the puncture of elimination reveals a normal spinal fluid the patient is considered as provisionally cured for a period of 6 months and then is subjected to a puncture of 1st control. If the result of this is favourable he is subjected to two further punctures at intervals of 6 months, and then if the fluid is still normal he is regarded as definitely cured. If the puncture of control gives an unfavourable result the patient is again put on treatment and further punctures of elimination and control performed according to the above scheme.

In order to combat arsenic resistance which has been recorded by various medical officers, it was decided to add germanin to the tryponarsyl usually given and to increase the dose of the arsenical. Two types of treatment were used :—The first is that recommended by VAN HOOF, viz. : recent cases : 1 gm. of germanin followed 2 or 3 days later by 4·5 gm. of tryponarsyl, and then at weekly intervals two further injections of tryponarsyl with sodium hyposulphite ; grave advanced cases : 1 gm. of germanin followed 3 or 4 days later by 4 gm. of tryponarsyl with sodium hyposulphite, then at weekly intervals 2 gm. of tryponarsyl up to a total of 24 gm. The second line of treatment is that advocated by RODHAIN and consists of 2 doses of 1 gm. of germanin on consecutive days followed by a series of injections of tryponarsyl according to the preceding scheme.

In all, 620,549 persons have been examined and 15,285 patients treated, but nothing is to be gained by analysis of these totals as certain places had not been examined previously. The Lower Congo has, however, now been under investigation by Foreami for 2½ years, and consequently it is possible to compare the state of affairs in 1933 with that of previous years. Among the 548,556 persons examined, 1,646 new patients were discovered ; this gives a contagious index of 0·30 per cent. as compared with 0·59 per cent. for 1931 and 0·41 per cent. for 1932.

The number of patients remaining on treatment on 31st Dec., 1932, was 6,212 as against 7,288 in 1931 ; that of patients put again on treatment was 1,262 as against 1,404 in 1932. The total number of patients treated was 9,120 as compared with 12,301 in 1931, and 10,873 in 1932. The endemic index was thus 1·66 per cent. in 1933, as against 2·45 per cent. in 1931 and 2·08 in 1932. The number of provisionally cured patients was 4,934 as against 3,855 in 1932.

Efficacy rate $= \frac{\text{cured} \times 100}{\text{number treated}} = \frac{4934 \times 100}{9120} = 54{\cdot}1$. In 1932 this figure was only 35·5.

The number of patients who disappeared was 354 in 1933, and 381 in 1932; of those who died 301 as compared with 340. Some 3,531 patients remained on treatment on 31st Dec., 1933, the maintained endemic index thus being 0·64 per cent. as against 1·55 per cent. for 1931 and 1·2 per cent. for 1932.

Having summarized in this way the total results obtained, Dupuy passes to an analysis of the results in the various subsectors. An interesting table is given regarding the efficacy of treatment=

$$\frac{\text{cured under control} \times 100}{\text{number treated.}}$$

This figure had improved considerably in all the subsectors except Mayumbe and Lufimi where treatment was handicapped by the existence of chronic arsenic-resistant cases.

After giving some interesting information regarding the results of lumbar puncture, Dupuy passes to the subject of arsenic resistance. This has now been recognized at various foci, viz., Mayumbe 71 new cases in 1933, Cataractes-Nord 7 new cases, Cataractes-Sud 35 new cases, and Lufimi-Basse-Sele 4 new cases. The total of new arsenic resistant cases discovered during the year was thus 121.

The last portion of this long report is concerned with details regarding the various subsectors and must be consulted in the original by those interested. *W. Y.*

JAMOT (E.). Note sur la maladie du sommeil en A. O. F. [**S.S. in French West Africa.**]—*Bull. Soc. Path. Exot.* 1935. June 12. Vol. 28. No. 6. pp. 499–507.

In 1920 a Commission, presided over by LAVERAN, published a detailed account of the position of sleeping sickness in the French West African Colonies. At that time the disease was recognized in French Guinea, in the Ivory Coast, and in parts of Senegal. Isolated cases had been found in Dahomey and the disease had also been recognized at certain places in Haut-Sénégal Niger. In 1926 HERIVAUX disovered the great focus in Togo which extended to Dahomey, and in 1931 SOREL and ROBINEAU drew attention to the fact that the disease was endemo-epidemic in Haute-Volta, in Dahomey, and on the Niger.

In this paper Jamot summarizes the situation as it exists in the various French West African Colonies at the present time. After dealing with each of the Colonies separately he states that the total number of cases recognized on 31st Dec., 1934, was more than 50,000. They are distributed as follows:—Niger 369, Soudan 2,580, Guinea 4,002, Dahomey 6,331 and Ivory Coast 38,167. If to these are added the 16,000 patients found in Togo in May, 1934, the total figure for French West Africa is no less than 68,000 [? 66,000]. When it is remembered that only part of the infected regions have been visited, that in the Ivory Coast which has been most investigated not more than two-thirds of the people have been examined, and that the limitations of the method of examination must allow many cases to escape recognition, it is obvious that the true figure is much greater than 68,000.

W. Y.

BEVAN (Ll. E. W.). **Notes on the Human Trypanosomiasis of Southern Rhodesia.**—*Jl. Comp. Path. & Therap.* 1935. June. Vol. 48. No. 2. pp. 97–111. [20 refs.]

After giving a general account of the development of knowledge of sleeping sickness due to *T. rhodesiense* since its discovery in November, 1909, the author passes to a consideration of human trypanosomiasis in Southern Rhodesia. Since 1912, there have apparently been only 7 European cases, all of whom contracted the disease in the Sebungwe and West Hartley districts. No cases have been recorded from the Lomagondi and Darwin districts in parts of which *G. morsitans* are plentiful, and where the author has found domestic animals to become infected with the *brucei* type of trypanosome. During the same period 49 native cases have been recorded.

During the last two years some alarm has been caused by the death from trypanosomiasis of a European, Mr. L —, who is believed to have contracted the infection at Gowe. Another European, Mr. A—, also developed the disease in this neighbourhood. During 1933 a number of cases of sleeping sickness were met with amongst native hunters in the Gowe district. Having thus located Gowe as the focus of recent infection, it is interesting to note that, according to the Chief Entomologist, there are certain small areas depicted in his maps where the tsetse fly survived after the rinderpest in 1896 ; and the Gowe area is one of these. Another such area is the Manzituba Vlei and environs in the Sebungwe district, and it is in this vicinity that the medical expedition of 1913 found its cases.

Bevan believes that it is in these places that the local natives would be liable to infection from birth and any premunity would be maintained by constant re-infection. It is in such places that one would expect to find carriers, and as a matter of fact carriers were actually found in these districts by the Commisssion of 1913 and by Dr. BLAIR in 1934. Other parts of the country appear to be free from human trypanosomiasis, and it is probable that with the clearing up of these comparatively limited areas this undesirable menace will soon be entirely eliminated from Southern Rhodesia. *W. Y.*

LESTER (H. M. O.). **Report of the Tsetse Investigation.**—*Nigeria Rep. Med. & Health Services for Year 1933.* Appendix B. pp. 74–83.

Topics discussed here are:—Tartar emetic treatment of cattle ; histopathology of bovine trypanosomiasis ; relation of *T. gambiense* and *T. rhodesiense* ; tsetse surveys ; testing of new drugs ; infection rates in man in Nigeria and measures to cope with the spread of infection.

During the year there have been further big increases in the amount of sleeping sickness work done in the field in Nigeria, and as far as possible research has been continued in the Gadau laboratories, although only a skeleton research staff is at work there. In May, Dr. NASH, Entomologist, joined the investigation.

Further experiments have been conducted on the treatment by tartar emetic of cattle infected with *T. congolense* and *T. vivax*. The results are disappointing. At the request of the Chief Veterinary Officer a small experiment was carried out to test the possibility of transmitting bovine trypanosomiasis directly from one animal to

another by means of an unwashed hypodermic needle. A " record " needle was inserted into the muscles of an ox, the blood of which contained numerous *T. vivax*. It was then removed and inserted immediately subcutaneously into a clean animal and subsequently into a second clean animal ; both became infected.

Dr. MERRETT has continued work on the histopathology of bovine trypanosomiasis (*T. vivax* and *T. congolense*). The post-mortem findings were extremely variable, but sufficient constant features were present to warrant a division into (*a*) completely negative autopsy, (*b*) slight involvement of the heart, and (*c*) marked cardiac lesions, associated with variable changes in other organs. Tissues from all the organs were sectioned and examined microscopically. Changes in the brain were not seen. The heart was the organ chiefly affected, showing all changes of myocarditis up to a condition of fibrosis and muscular fragmentation.

Work on the characteristics of Nigerian strains of the polymorphic trypanosomes has been continued. In all, 17 such strains have been investigated, and it has been found that certain strains exhibited characteristics intermediate between *T. rhodesiense* and *T. gambiense*. As a result of this work it is believed that *T. rhodesiense* is only a virulent type of *T. gambiense*. A full report has already been published [this *Bulletin*, Vol. 31, p. 198].

An attempt is being made to maintain various strains of trypanosomes by constant cyclical transmission through *G. tachinoides* and *G. morsitans*. The characters which are being investigated are virulence to small laboratory animals and reaction to tryparsamide.

The Entomologist has carried out tsetse surveys, and as the result of a prolonged tour through the south-eastern and southern districts of Kano Emirate recommendations have been made for a number of local clearings intended to reduce fly-man contact to a minimum. It is believed that judicious clearing of narrow belts of riverine vegetation would reduce the incidence of sleeping sickness in these areas to very small proportions ; frequently, the existence of *G. tachinoides* depended upon a belt of quite light vegetation, which in many cases was only 10 yards in width. Research is being carried on with the object of studying the relationship between tsetse and different types of vegetation, and to ascertain the reasons for the tsetse preferences by measuring the climatic conditions in favourable and less favourable vegetation types.

The testing of new chemical compounds.—A system of co-operation with certain large chemical firms in Europe has been inaugurated, and arrangements have been made for promising new drugs to be sent to Gadau to be tested against freshly isolated strains. If the results seem encouraging, the drugs will then be tested against human and animal trypanosomiasis in the field.

Observations have been made on two new chemical compounds supplied by Messrs. Bayer-Meister Lucius. The first of these, Surfen C, a quinoline derivative, was found to be very active in laboratory animals infected with trypanosome strains isolated from man ; but in man himself the strains did not appear to be nearly so sensitive, and the use of the drug in human trypanosomiasis is contra-indicated, as it is liable to produce acute nephritis. The drug is being tested against *T. vivax* and *T. congolense*, and it seems possible that it may prove to be a valuable remedy in animal trypanosomiasis.

Experiments have been started with the second drug Std. 386B, an organic compound of arsenic and antimony. The results are, as yet, incomplete.

The next portion of the report summarizes the work on sleeping sickness. During the year, 27,919 cases of sleeping sickness have been treated. To begin with there were three sleeping sickness teams in the field, but by the end of 1933 five complete teams, each consisting of one medical officer, two nurses and 24 dispensing attendants, were at work, whilst a 6th team was due to start in January, 1934. Part of this service has been paid for by the Native Administrations.

The infection rates which have been found give some indication of the magnitude of the problem with which they have to deal. In various districts this ranges from 16 to 29 per cent. There is a good deal of indirect evidence to show that the disease has spread rapidly during the last few years. In many areas the death rate has been high and there has been a definite decrease in the population, especially in the Zaria Emirate, where shrinkage in the population has been alarming.

An attempt is being made to cope with the disease by mass treatment and by localized protective measures against the tsetse fly. Experience has shown that mass treatment itself is quite effective in reducing the incidence of the disease. Ellis, working in Hadeija, found that of 829 positive cases which had been given a course of 23 gm. of tryparsamide, only 15, *i.e.*, 1·8 per cent., had trypanosomes in their gland juice or blood at the end of treatment. In other parts of the country, however, many more cases had been found to be resistant to treatment with tryparsamide. For this reason arrangements had been made to use a combined treatment of antrypol and tryparsamide on a large scale.

The article closes with a detailed report of Dr. Paisley, the Senior Sleeping Sickness Officer. *W. Y.*

Dumont (Robert). Influence des conditions alimentaires sur la gravité et l'extension de la maladie du sommeil. [**The Influence of the Food Supply on the Gravity and Extension of Sleeping Sickness.**]—*Rev. Méd. et Hyg. Trop.* 1935. Jan.–Feb. Vol. 27. No. 1. pp. 36–37.

In this note the author stresses the importance of nutrition in a combat against sleeping sickness. He quotes from Huot (1924) to the effect that insufficient crops with malnutrition is a condition constantly found in all places gravely infested by sleeping sickness, and furthermore that it appears that trypanosomiasis does not kill in populations normally nourished.

Martin concluded that under-feeding of the natives greatly increased the evil effects of trypanosomiasis. Jamot cites a striking example. In the valley of the Koumi, 9 villages at the beginning of 1913 contained 5,933 inhabitants. Towards the middle of the year, the first cases of sleeping sickness were imported. In 1924, Poux records that the population was industrious and prolific and covered the country with magnificent plantations. In this region sleeping sickness had not done much harm. There are two factors which play a part in the epidemiology of the disease—the parasite and the resistance of the subject. Other examples are given.

Dumont concludes that in the combat against sleeping sickness one should not rely entirely on medicaments, no matter how active

they may be, but also on the resistance of the organism conferred by good feeding. *W. Y.*

Duke (H. Lyndhurst). **On *Trypanosoma brucei*, *T. rhodesiense* and *T. gambiense* and their Ability to Infect Man.**—*Parasitology.* 1935. Feb. Vol. 27. No. 1. pp. 46–67. [30 refs.]

In this work the author has continued his inquiry into the relationships of the African polymorphic trypanosomes to one another and to man. He has worked with 11 strains and has examined the transmissibility of each by *G. palpalis*, and also the power of each to infect man, after it had been maintained in the laboratory for various periods and by different methods. The results of his observations are summarized as follows :—

" 1. A strain of *T. rhodesiense* [Tinde III], isolated from man and readily transmissible by tsetse, was passed by direct inoculation through a series of fourteen guineapigs over a period of 18 months. At the end of that time it had lost its transmissibility by *Glossina palpalis*, and it also failed to infect a volunteer.

" 2. Another line of the same strain, after 98 days in a bushbuck, 30 days in a fowl and 294 days in oxen, proved still readily transmissible by *G. palpalis* and also readily infective to man.

" 3. A second strain [Tinde I] underwent seven consecutive cyclical passages through tsetse, then two passages by the syringe, and finally another cyclical passage, all save one in monkeys. When tested on man at the tenth and eleventh passages it was found to be non-infective.

" 4. A strain of *T. gambiense* [Braun], isolated in November 1920 from a patient from Fernando Po, was found in February 1934 to be readily infective to man. The strain was entirely non-transmissible by and almost completely non-infective to *G. palpalis*.

" 5. Three strains of *T. brucei* [LV, LVI, LVII], one from the west, one from the north and one from the south of Uganda Protectorate, were found to be incapable of infecting normal healthy man. All the tests were carried out with cyclically infected tsetse.

" 6. A freshly isolated strain of *T. gambiense* [LII] from a Uganda native was transmitted to man by cyclically infected laboratory-bred *G. palpalis*.

" 7. A strain of *T. rhodesiense* [LX], shortly after its recovery from a native of Tanganyika Territory, underwent three successive cyclical passages by laboratory-bred *G. palpalis* from monkey to monkey ; at each passage the strain was tested on man and found to be readily infective.

" 8. A strain from Nigeria [BR] showing points of resemblance to both *T. gambiense* and *T. rhodesiense* was found to be pathogenic to man, on subcutaneous inoculation of infected blood, three years after its first isolation."

Duke lays stress on the fact that this work constitutes the first record of the experimental infection of man either with *T. gambiense* or with *T. rhodesiense* by the bite of a cyclically infected tsetse. It also contains an account of the loss by two accredited strains of *T. rhodesiense* of the power to infect man. The fact that *T. rhodesiense*, under conditions which may reasonably be described as natural, may lose its power of infecting man is of considerable interest. The possibility was to some extent fore-shadowed by the work of the reviewer and his colleagues [this *Bulletin*, Vol. 27, p. 804], but the only reliable criterion in the matter is the test on the human subject applied as nearly as possible in the way nature applies it.

The loss of pathogenicity to man by strain Tinde III is the first substantiated record of this phenomenon. Duke states that this is

apparently ascribable to the effect of passage through guineapigs, for under different conditions the strain retained this property. Reference is made to the fact that CORSON has found that a strain of *T. rhodesiense* was still pathogenic to man after maintenance in goats by direct inoculation for a period of 19 months ; and also to the fact that CORSON in a later paper refers to the increased susceptibility to human serum caused by guineapigs. There is thus some evidence that maintenance of a trypanosome in guineapigs has an unfavourable effect on certain of its activities, viz., reducing its transmissibility by Glossina and probably impairing its ability to infect man.

Although after passage through the guineapigs the infectivity of strain Tinde III to *G. palpalis* was diminished enormously, passage through oxen produced no such effect. This is especially interesting in light of Duke's previous experience of the effect on man's trypanosomes of sojourn in calves : in these experiments the indices of a strain examined in the blood of a calf were invariably reduced [this *Bulletin*, Vol. 31, p. 566].

The striking contrast between the behaviour of the *T. gambiense* strain (Braun) and that of Tinde III in guineapigs is a matter of interest. Prolonged residence in small laboratory animals, extending over 14 years, had failed to impair the pathogenicity of the former strain for man, although the strain had completely lost its transmissibility by *G. palpalis*. The observations indicate the relative antiquity of *T. gambiense* as a parasite of man and the comparative instability of the power of *T. rhodesiense* to infect man, and show how easily this trypanosome may revert to a form indistinguishable from typical "wild" *T. brucei*. These facts tell against KLEINE's hypothesis that *T. gambiense* and *T. rhodesiense* are one and the same species, zoologically distinct from *T. brucei*. Duke finds in the present observations support for the view advanced by him in 1921, viz., " *T. gambiense*, *T. rhodesiense* and *T. nigeriense* are to be regarded as particular strains of *T. brucei* which have become, after sojourn in other hosts, more or less adapted to life in the blood of man."

No one has yet witnessed the exhibition by an unequivocal *T. brucei* of the power to infect man, but the issue is confused by the convention whereby any *T. brucei*-like trypanosome recovered from game or wild tsetse, and proved capable of infecting man, is at once styled *T. rhodesiense* and assumed to have had previous acquaintance with man. Duke states that he has long believed that there are in nature strains of *T. brucei* which, given the opportunity, can use man as a host, and it is now quite certain that a trypanosome can and does change in relation to a particular host, *i.e.*, man. TAUTE's big experiment in which 129 natives, including weaklings and diseased, withstood exposure to 6 strains of *T. brucei* seems to Duke to justify the conclusion that if man is to become infected by *T. brucei* the onus is on the trypanosome to overcome some degrees at least of the range of resistance possessed by a normal human community.

Duke believes that the resistance of man to *T. brucei*, though considerable, is not absolute, and in *palpalis* regions man has paid the penalty of this imperfection by becoming the principal mammalian host for the representative of *T. brucei* in those regions, *T. gambiense*. The paper concludes as follows :—

" As matters stand at present, the claim of *T. rhodesiense* to distinction as a species, or even a subspecies, is indeed feeble. The name is, however, useful until it is decided whether *T. brucei* or *T. gambiense* can best absorb

it zoologically. The evidence recently acquired at Entebbe seems to me to identify this trypanosome with *T. brucei*. If this be the correct interpretation, then the two types of human trypanosomiasis are to be ascribed to *T. gambiense* and to *T. brucei* respectively. For the former trypanosome, by virtue of its long establishment as a parasite essentially dependent on man in primitive African conditions, surely possesses a fair claim at all events to 'dominion status' if not to complete severance from its parent stock." *W. Y.*

DUKE (H. Lyndhurst). **Further Studies of the Behaviour of *T. rhodesiense*, recently isolated from Man, in Antelope and Other African Game Animals.**—*Parasitology.* 1935. Feb. Vol. 27. No. 1. pp. 68–92. [20 refs.]

The work dealt with in this paper is a continuation of similar work published in 1933 [this *Bulletin*, Vol. 30, p. 769]. Its object is to determine the effect on the trypanosomes of man of prolonged residence in antelope. Duke has had two main questions in mind; firstly, whether prolonged residence in antelope interferes with the power of the trypanosome to infect cyclically Glossina; and secondly, whether it interferes with the capacity of the trypanosome to infect man.

After briefly reviewing previous work bearing on these important problems, Duke passes to a detailed account of his own work. The following summary is given:—

"1. Evidence is produced to show that *T. rhodesiense* may retain its cyclical transmissibility by *Glossina* for at least 600 days in an antelope.

"2. Prolonged residence in these animals tends to impair the power of a strain to infect man, when infection is attempted by the cyclical route. Thus of six volunteers exposed to cyclically infected tsetse carrying *T. rhodesiense* that had been for many months continuously in antelope, only one became infected. *All these flies derived their infections from the antelope itself.* As the cyclical method is the one operating in nature, these observations suggest that although certain species of antelope are admirable hosts for *T. rhodesiense*, yet as a reservoir from which tsetse can become infected with trypanosomes pathogenic to man these animals do not constitute so great a menace as has hitherto been supposed.

"3. In contrast to (2), in every instance where the trypanosomes from the antelope, before being tested on man, were inoculated by the syringe into a monkey, every volunteer exposed became infected.

"In the single experiment where the monkey was infected by tsetse instead of by direct inoculation from the antelope, one volunteer became infected and another did not. There is thus a suggestion that the passage through the monkey prepared the trypanosome for survival in man. On the other hand, the behaviour of strain Tinde I shows that *T. rhodesiense* may lose its power to infect man in spite of repeated passage through monkeys.

"4. Some further indirect evidence is produced to show that *T. rhodesiense* may owe its origin to *T. brucei*, and that pathogenicity to man may be a property possessed in different degrees by different strains of *T. brucei* in nature.

"5. These researches suggest, also, that human beings differ in their susceptibility to *T. rhodesiense*, but that these differences only operate within a narrow range of variation in the power of strains to infect man. In other words, strains strongly pathogenic to man will infect anyone,

but strains whose power has been weakened will only be able to use individuals of subnormal resistance.

" 6. Two different strains of *T. rhodesiense* have been shown to behave differently in the same man. One did and the other did not infect him.

" 7. There may be a difference in the suitability of the various species of antelope to act as hosts to *T. rhodesiense*. Thus the bushbuck seems to be a better host to the trypanosome than the oribi.

" 8. A young hyaena infected with *T. rhodesiense* for 180 days remained in excellent health. Flies infected from a monkey sub-inoculated with the blood of this hyaena infected a volunteer : the trypanosome had then been 80 days in the hyaena.

" 9. Clean flies that had taken their first two meals off monkeys infected with a strain of *T. rhodesiense* non-pathogenic to man, were nourished entirely on human blood during the first 3 weeks of the cycle of development of the trypanosomes in their interior. These flies, on the completion of this cycle, were still unable to infect man.

" 10. A strain of *T. rhodesiense*, after a series of cyclical passages through a reedbuck and six monkeys, was found to be non-pathogenic to man. The possibility has to be borne in mind that this strain owed its original association with man to meeting an abnormally susceptible individual. This strain since its arrival at the Institute has been tested on nine different volunteers, and none of them became infected. There is therefore nothing to distinguish it from *T. brucei*, save the fact of its isolation from man.

" 11. It is recorded that a single cyclically infected fly infected a volunteer at a single feed.

" 12. It is shown that the appearance of a tender indurated swelling at the site of the bite of an infective fly is a not uncommon symptom of an infection with *T. rhodesiense*. Local tenderness and swelling were also noted where the glands of an infected fly had been inoculated subcutaneously, even in cases where no infection ensued. Where inoculations of blood were employed on man the local disturbance disappeared rapidly when no infection resulted, but when infection took place the local symptoms steadily increased during the last few days of the incubation period, and before trypanosomes were recognized in the peripheral blood.

" 13. The only infection of an antelope with *T. gambiense* carried out during this research was that of oribi III with strain LI. This strain at its first isolation was not very transmissible by *G. palpalis*, and after a few months in the antelope showed signs of failure to adjust itself of this particular host. Another strain, mentioned in a previous paper (Duke, 1935), failed to infect an adult female situtunga, although two sheep exposed to the same strain at the same time duly became infected."

W. Y.

Duke (H. Lyndhurst). **Studies on the Factors that may Influence the Transmission of the Polymorphic Trypanosomes by Tsetse. IX.—On the Infectivity to *Glossina* of the Trypanosome in the Blood of the Mammal.**—*Ann. Trop. Med. & Parasit.* 1935. July 17. Vol. 29. No. 2. pp. 131–143.

In this paper Duke gives a selection of the various transmission experiments carried out at Entebbe which, in his opinion, illustrate what appear to be different phases of the phenomenon of transmissibility. Robertson (1912) wrote " Given reasonably favourable conditions of temperature and moisture, it is the strain of trypanosomes and not the fly that within a relatively wide range plays the deciding

rôle in limiting the number of infected glossina." Duke states that in his earlier work he adopted as a working hypothesis the assumption that there are certain forms of the trypanosome in the mammal especially fitted to infect tsetse, and that when a fly takes up a sufficient number of these forms it becomes infected. More recent experience showed, however, that the problem is by no means so simple. The part played by the fly is undoubtedly of considerable importance, and TAYLOR (1932) has produced evidence that temperature also exerts an influence.

During 15 years of experimental work, Duke has acquired certain impressions regarding the laws which govern the transmission of trypanosomes by tsetse. He considers that he has demonstrated that there exist in nature in Africa strains of trypanosomes which, at the time of their original isolation from the vertebrate, man or antelope, are non-transmissible by *G. palpalis*. Such strains remain consistently non-transmissible. The disappearance of transmissibility has actually been witnessed in a number of strains of *T. gambiense* during their maintenance in the laboratory. These observations all point to an inherent and permanent change in the trypanosome itself, quite unconnected with the variability of the insect vector.

Four series of transmission experiments are discussed in the present paper. Series I consist of paired experiments. Two batches of flies were fed at the same time on the same infected animal; thereafter one of the batches was nourished on a clean animal, while the other was fed again on one or more occasions on an infected animal. In Series II each of the tests consisted of 4 or 5 experiments instead of a pair as in Series I. The flies of one experiment of each test fed on 3 or 4 different days on the infected animal, and on each of these days a box of clean flies fed on the same animal only once. The general conclusion from these two series of experiments is that they furnish no evidence that multiple feeding results in a higher infection rate than does single feeding.

The experiments of Series III represent another attempt to raise the infection rate of *G. palpalis* by repeated exposure to the chance of infection. The results confirm the conclusion reached from the first two series of experiments.

The experiments grouped into Series IV were selected from the records of the Entebbe Institute to illustrate various phenomena of common occurrence. They are summarized in a table which is divided into four sections. Section A illustrates consistent infectivity of the trypanosome to tsetse; Section B illustrates periods of intensified activity; Section C illustrates non-infective periods, and Section D illustrates the results of feeding flies on man for several consecutive days; a fresh box of flies being fed each day.

The author's conclusions are as follows:—

"1. A study of the Entebbe records of transmission experiments with man's trypanosomes and *G. palpalis* lends support to Robertson's views on the endogenous cycle expressed in 1912.

"Of special interest is the evidence of the existence of 'negative phases' in the development of the trypanosome in the mammal, phases during which the trypanosomes though often numerous in the blood are non-infective to the tsetse.

"2. An examination of the experimental section of this paper suggests that repeated feeds on an infected animal during a positive phase of the cycle do not increase the infection rate of the flies over that produced by one such feed." *W. Y.*

i. Borremans (P.) & van Bogaert (L.). Les manifestations extra-pyramidales de la trypanosomiase chez l'Européen. (Syndrome d'inhibition avec stéréotypies, pigmentations cutanées symétriques et anneau cornéen.) [**Cases of Extra-pyramidal Syndrome and Psychosis in S.S.**]—*Jl. Belge Neurol. et Psych.* 1933. Vol. 33. No. 8. pp. 561–588. With 12 figs. [38 refs.]

ii. Baonville (H.), Ley (J.) & Titeca (J.). Psychose hallucinatoire chez un trypanosomié.—*Ibid.* 1934. Feb. Vol. 34. No. 2. pp. 129–138.

i. A detailed clinical account is given of a patient who exhibited a particularly well marked extra-pyramidal syndrome. The case is assumed to be one of trypanosomiasis, but the diagnosis appears to be based on the clinical history and the pathological findings at the autopsy ; there is no evidence that a definite diagnosis was ever made.

The patient had spent 12 years in Uganda and Urundi. During 1927, he had two severe febrile attacks and pronounced erythema of the abdomen and lower extremities. These attacks were accompanied by severe headache, but there is no record of any adenitis ; lumbar puncture was not performed. In 1929 the patient became very irritable ; he manifested violent paroxysms of anger, especially when in an alcoholic condition ; he slept badly and became very emaciated. During his last year in Africa he indulged in sexual excesses of all sorts and in sadism, and had a severe attack of dysentery. A course of neosalvarsan was given without benefit and he was invalided home. Shortly after his arrival in Belgium, things became worse. He exhibited visual hallucinations and later mental confusion and somnolence. Sphincter trouble finally developed and the patient owing to his obscenities and violence had to be put in a mental home. Lumbar puncture gave a negative Wassermann, protein : 1·04 gm., Pandy : +++, lymphocytosis : 113. As he became a little better he was discharged, but had to be re-admitted two months later. Blood examinations were negative and arsenical treatment was of no avail.

During his second sojourn in hospital, the patient exhibited several epileptiform attacks. He lay on his back with his limbs completely extended for hours without making any movement. When spoken to, he replied correctly in a monotonous voice ; there was a complete absence of spontaneity, and he made only those movements which were absolutely necessary. There were no tremors but a permanent hypertonic state of the muscles. Examination of the eyes was interesting ; the cornea was surrounded by a greenish-brown pigmented circle, but the movement of the eyes was completely normal and the pupils reacted normally. All the cranial nerves were intact ; the reflexes were normal as was also sensation. He was habitually in a torpid mental state, and it was only during the acute periods that there was a tendency towards paranoia. There was very deep brown pigmentation of the skin of the legs and feet, which stopped at the level of the prominence of the tibia ; the penis was similarly pigmented.

The condition remained more or less like this for 3 months when there was a sudden febrile disturbance with dyspnoea and death.

There follows a lengthy account of the post-mortem findings ; these consisted of a meningo-encephalitis with pronounced meningeal infiltration, and an intense infiltration of the central grey nuclei.

The findings in this case are compared in detail with those of other observers and the conclusion is reached that the case was one of trypanosomiasis.

ii. A description is given of a case which exhibited a paranoid syndrome and which, from the history and development of the disease, was believed to be one of trypanosomiasis.

It is noted that the patient—a native of the Belgian Congo—left Africa in 1922 and remained in Europe in a state of apparent good health for 10 years. Delusions of persecution then developed insidiously. A lengthy clinical account of the case is given and this is followed by a discussion regarding the correct diagnosis. [These papers must be consulted in the original by those interested.] *W. Y.*

RASKIN (A.). **The Clinical Aspect of Trypanosomiasis.**—*Med. Parasit. & Parasitic Dis.* Moscow. 1935. Vol. 4. No. 1–2. [In Russian pp. 117–120. English summary p. 120.]

A detailed description of the clinical course and treatment of a case of human trypanosomiasis contracted by an accidental laboratory infection with a mouse-strain of *T. gambiense*. The incubation period in this case was 8 days. The patient was successfully treated with "Bayer 205" combined with neosalvarsan. *C. A. Hoare.*

VAN SLYPE (W.). Instabilité liquidienne de certains trypanosés traités par la tryparsamide. [**Instability of the Cerebrospinal Fluid in Cases of Trypanosomiasis treated with Tryparsamide.**]—*Bull. Soc. Path. Exot.* 1935. June 12. Vol. 28. No. 6. pp. 432–434.

In the course of treating 378 sleeping sickness patients with tryparsamide, the author encountered five in whom the changes in the spinal fluid were peculiar. Details of the treatment and of the cell contents of the spinal fluid found at 3 subsequent lumbar punctures are given. In 4 of the 5 cases the lumbar puncture made immediately after treatment showed an excess of cells, whereas the punctures made 1 to 3 months later revealed in every case a normal cell count. The third puncture made 3 to 5 months after the second showed in all cases but one an excess of cells.

The author inquires whether these changes can be explained on the following hypothesis:—The excess of cells found at the first puncture is due to a meningeal reaction caused by the drug; this disappears after a month or two and hence the second puncture is normal, whilst the abnormal findings at the third puncture are the result of a nervous relapse due to the infection. On such a hypothesis it is curious that those cases which exhibit a meningeal reaction to the drug should likewise relapse. Are we concerned here with individuals possessed of a peculiarly fragile nervous system, especially sensitive to tryparsamide and at the same time especially liable to relapse? It is unlikely that all these successive changes are due to tryparsamide alone, because a second course of tryparsamide made the spinal fluid normal.

The conclusion reached is that a certain small number of cases of sleeping sickness exhibit an unstable spinal fluid after treatment with tryparsamide, and that consequently several punctures at intervals of several months should be performed after treatment as a second course may prove to be necessary. Details are given of 5 other cases in which so far only 2 post-treatment punctures have been made, but which the evidence so far collected suggests fall into the same category as the above cases. The author therefore believes that 9 of his 378 cases exhibit what he designates as instability of the spinal fluid, *i.e.*, a normal post-treatment puncture sandwiched between two abnormal punctures. *W. Y.*

Schwetz (J.). Sur un nouveau cas de trypanosomiase (humaine) arsénico-résistante. [**New Arsenic Resistant Case of Sleeping Sickness.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Mar. Vol. 39. No. 3. pp. 123–125.

Information is given regarding a case of trypanosomiasis which was resistant to tryparsamide, but susceptible to fouadin.

The patient, who came from the region of Stanleyville, was diagnosed as suffering from trypanosomiasis on the 3rd December, 1932. From the 4th to the 24th December he was given 7 gm. of tryponarsyl. On the 2nd January, 1933, a lumbar puncture revealed 3·4 lymphocytes per cmm. When examined at the laboratory at Stanleyville on the 9th February, 1933, no puncturable glands were found, but fresh preparations of his blood showed numerous trypanosomes. Between the 7th March and the 3rd July, 1933, the patient was given 36 gm. of tryparsamide. On the 5th July there were no puncturable glands, but two trypanosomes were found in 10 cc. of blood examined by the triple centrifugation method. The patient was then put on a course of fouadin, and between the 17th July and the 10th August, 1933, he received 10 injections. Examinations made on the 21st August and the 23rd September were completely negative. *W. Y.*

de Marqueissac (Henri). Emploi des principaux médicaments spécifiques dans le traitement de la maladie du sommeil et utilisation de ces médicaments dans les traitements associés. [**The Use of the Chief Specific Drugs in the Treatment of Sleeping Sickness and the Employment of these Drugs in Combination.**]—*Gaz. hebd. Sci. Méd. de Bordeaux.* 1935. Jan. 27 & Feb. 3. Vol. 56. Nos. 4 & 5. pp. 56–60; 67–71.

These papers give an account of the various drugs used in the different forms and stages of human trypanosomiasis and discuss the various indications for the employment of the particular drugs, and the various signs of intoxication which they may produce. The articles are of general interest to the practitioner but contain nothing new, and do not require special mention in this *Bulletin*. *W. Y.*

van den Branden (F.) & Appelmans (M.). Au sujet du tryponurile. [**On Tryponurile.**]—*Ann. Soc. Belge de Méd. Trop.* 1935. Mar. 31. Vol. 15. No. 1. pp. 107–112. [12 refs.]

Tryponurile (Meurice) is a product prepared by l'Union Chimique containing equal parts of tryponarsyl and hexamethylene tetramine. It may produce kidney lesions.

The authors gave 5 rabbits an injection of 2 gm. of this preparation. The animals were kept under observation for 15 days and all remained alive. The urine was collected and examined, and in that of 2 rabbits albumen was found. The rabbits were then killed and the kidneys examined. Pronounced degeneration of the epithelium of the uriniferous tubules was discovered in all 5 animals. In 2 other rabbits, which had been given an injection of 1 gm. of tryponarsyl only, similar lesions were found, but they were not so pronounced and were more discrete.

A summary of the literature relating to the administration of tryponurile to man is given. The general conclusion reached is that in view of the accidents which had been observed in man, and of the

renal lesions which were found in rabbits, tryponurile must be given with caution in the treatment of human trypanosomiasis. Van den Branden is of opinion that the initial dose of tryponurile for man should not exceed 4 gm. *W. Y.*

Silberschmidt (W.). Ueber Chemotherapie durch Inhalation. Versuche mit Trypanosomen. [**Chemotherapy of Trypanosome Infections through Inhalation.**]—*Schweiz. Med. Woch.* 1935. June 15. Vol. 65. No. 24. pp. 551–553.

The object of the experiments described in this paper was to ascertain whether inhalation-therapy was of any use in infectious diseases. The author selected as his experimental infection *T. evansi* in rats and mice, and tartar emetic as the drug to be examined.

The tartar emetic solution was sprayed by means of a water-pump into a 25 litre triangular box, the apex of which was covered with glass. The experimental animal was placed in an open cage at the bottom of the box. The strength of the tartar emetic solution varied from 1 to 5 per cent. and 3 cc. were sprayed into the box within an hour. How much was inhaled by the animal and how much was deposited on the sides of the container, it is impossible to say. The animals were exposed to the spray for 2 to 6 hours once or twice daily for several weeks ; some died of dysentery (antimony poisoning), but others tolerated the treatment for 4 weeks.

The results of the experiments, which are summarized in tables, show that the treatment controlled the infection and prolonged the life of the rats and mice very considerably (3–9 days for the controls, over 30 days for the treated animals) ; *therapia sterilisans magna* was, however, not obtained. *W. Y.*

Launoy (L.) & Prieur (M.). Contribution à l'étude de l'essai biologique de la tryparsamide. [**The Biological Testing of Tryparsamide.**]—*Bull. Soc. Path. Exot.* 1935. May 8. Vol. 28. No. 5. pp. 389–398.

Although tryparsamide is perfectly crystallizable and it exhibits constant physical and chemical properties, it is subjected to a biological control, which is essentially a test of its toxicity. This consists in the intravenous injection of 5 well-nourished adult male rabbits with a dose of 0·75 gm. per kilo. of tryparsamide in a 10 per cent. solution ; 3 of the 5 animals should survive without signs of serious intoxication. A period of observation is not stated, but is ordinarily 7 days. This control has been accepted by all firms possessing a licence from the Rockefeller Institute.

Reference is made to the work of Pottier & van den Branden [this *Bulletin*, Vol. 30, p. 786] who, working with the different brands of tryparsamide, found that rabbits easily tolerated a dose of 1·25 gm. per kilo., and that 100 per cent. of fatalities was obtained only when the dose was 2·5 gm. These authors accordingly suggested that for the efficient test the dose should be 1 gm. or 1·25 gm. instead of 0·75 gm. as hitherto.

During the period September, 1933, to March, 1935, the authors have had occasion to make numerous tests on the toxicity of tryparsamide. Most of their work has been done with the French product. They point out that before the biological investigations are undertaken,

a chemical analysis of the drug is essential. The drug should contain 24·6 to 25 per cent. arsenic ; it ought not to lose more than 0·5 to 0·6 per cent. of water after heating for 4 hours in the air at a temperature of 98°C. Anilarsinic acid should be present only in imponderable amounts.

The results of the authors' experiments on the toxicity of tryparsamide for a rabbit are summarized in tables. In all, 162 rabbits were given a dose of 0·75 gm. per kilo. and of these 75 per cent. survived 7 days, 70 per cent. 10 days, 59 per cent. 20 days, and 55 per cent. 30 days. The results obtained for the 308 rabbits which received 1 gm. per kilo were 57 per cent. alive after 7 days, 49 per cent. after 10 days, 41 per cent. after 20 days, and 39 per cent. after 30 days. It is pointed out that the differences obtained after 20 and 30 days of observation are very slight, but the differences between 7 and 10 days and 20 and 30 days are considerable. The conclusion is that the observation period should be 20 days, the usual 7 days being insufficient. The dose of 0·75 gm. gives more regular results than does the larger dose. It is probably therefore to be preferred.

The authors give an account of the technique used by them in the preparation of their solution of tryparsamide. In this they point out what is generally well known, viz.: that if one wishes to make a 10 per cent. solution of tryparsamide, he should not add 10 gm. of the drug to 100 cc. of water (the final volume of such a solution would be 107·75 cc.)

Information is next given regarding the toxicity of tryparsamide for mice. The results of an enormous number of experiments with the French product manufactured between 1933 and March, 1935, are summarized in the following table :—

Number of mice treated	Doses in cgm. per 20 gm. mouse	Percentage of survivals after 10 days	Percentage of survivals after 30 days
105	6	80	71
895	7	64	54
495	8	60	49
155	9	50	43
145	10	38	33

The paper ends with some observations on the trypanocidal action of tryparsamide on *T. brucei* infections in mice. *W. Y.*

Lourie (E. M.), Murgatroyd (Frederick) & Yorke (Warrington). **Studies in Chemotherapy. XII.—The Diffusibility of the Aromatic Arsenicals into Erythrocytes and the Action of the Latter on the Pentavalent Arsenicals.**—*Ann. Trop. Med. & Parasit.* 1935. July 17. Vol. 29. No. 2. pp. 265–282. [10 refs.]

These experiments show that the aromatic arsenicals, reduced tryparsamide and tryparsamide, diffuse into the red cells, that that part of the tryparsamide which enters the red cells is changed into a more actively trypanocidal substance, that a solution of red cells is capable of greatly increasing the trypanocidal power of tryparsamide, possibly by converting it into reduced tryparsamide, and that haemoglobin is not responsible for the change, which depends on a constituent that is relatively thermostable.

In the previous article of this series [*ante*, p. 26] the trypanocidal titre of the serum of rabbits was recorded after the intravenous injection of certain aromatic compounds of arsenic. It was found :—

" 1. That the effect of injection of an arsenobenzol compound (N.A.B.) or of an aromatic trivalent arsenical compound (reduced tryparsamide thioglycollate) is to confer immediately upon the serum an enormously high trypanocidal titre ; this titre, which is proportional to the dose given, immediately falls—quickly at first and more slowly later—until it ultimately returns to zero. The fall in the case of reduced tryparsamide thioglycollate is much more rapid than in that of novarsenobillon.

" 2. That the immediate effect of injection of an aromatic pentavalent arsenical compound (tryparsamide) is to confer but a relatively low trypanocidal titre upon the serum ; instead of falling, however, as happens with the other two drugs, the titre steadily rises and does not attain to its maximum for some time after injection. The titre reached is, moreover, in no way comparable with the enormous titres obtained with novarsenobillon and reduced tryparsamide thioglycollate. [These observations are illustrated by the graph on page 27, above.]

" 3. That, whereas in the case of the arsenobenzol compound the trypanocidal titre exhibited by the serum 2½ minutes after intravenous injection approximated fairly closely to the calculated value, in the case of the other two compounds the titres observed were only small fractions of the calculated values."

The authors asked themselves :—

" Why in the case of N.A.B. does the titre observed 2½ minutes after injection approximate to the calculated titre, whilst in the case of reduced tryparsamide thioglycollate it is only a small fraction of the calculated value ; . . . why during the hours which follow the injection does the titre fall so much more rapidly in the case of reduced tryparsamide than in that of novarsenobillon ? . . . Why . . . should the titre observed 2½ minutes after intravenous injection of tryparsamide prove to be only a small fraction of the calculated value, and why should the titre rise during the next 6 hours instead of falling as in the case of the other compounds ? "

The experiments were designed to answer these questions and had the results described in the summary, given here in part.

" It was found that, if red cells were suspended at 37°C. in a solution of reduced tryparsamide in either Ringer-glucose or ' nutrient medium,' a certain amount of the drug rapidly passed into the red cells. This was evident from the fact that when these red cells were laked, after separation from the drug solution and washing rapidly in large volumes of iced saline, the laked solution was powerfully trypanocidal. Furthermore, when drug-laden red cells, washed in iced saline, were subsequently suspended in Ringer-glucose or ' medium,' drug diffused out of the red cells into the surrounding fluid.

" The amount of reduced tryparsamide which diffused into red cells depended firstly on the concentration of the drug in the surrounding medium, and secondly, although to a much less extent, on the length of time the red cells were exposed to the solution of drug. When red cells were suspended for 15 minutes at 37°C. in an equal volume of Ringer-glucose-drug solution containing 1 : 25,000 reduced tryparsamide, the concentration of drug within them was found to be 1/4th to 1/8th of that in the surrounding fluid ; when the concentration of the drug was increased 16 times, *i.e.*, to 1 : 1,562·5, the concentration found in the red cells was about 1/16th of that of the surrounding fluid. The amount of drug which had diffused into the red cells within 24 hours was in each case about double that found within 15 minutes. It was immaterial whether the drug was dissolved in Ringer-glucose alone or in ' nutrient medium ' (equal parts of Ringer-glucose solution and rabbit serum heated to 64°C. for 30 minutes)."

" Similar experiments on the diffusibility into red cells of the pentavalent compound tryparsamide gave more complicated results. Whilst

there seemed to be no doubt that tryparsamide, like its reduced homologue, diffused readily into red cells, it became at once obvious that another factor was at work which largely obscured the main issue When red cells, which had been in contact for some hours with 0·5 per cent. solution of tryparsamide, and then washed thoroughly in iced saline, were suspended in drug-free Ringer-glucose solution, a substance was found to have diffused out of the red cells which was of enormously greater trypanocidal power than the 0·5 per cent. solution of tryparsamide. It is, therefore, clear that red cells are, in some way, able to change the relatively inert tryparsamide into a highly trypanocidal substance.

" This recalls certain interesting observations made many years ago by Levaditi, Yamanouchi and others. Levaditi and Yamanouchi (1908) showed that emulsions of liver, muscle and lung incubated with atoxyl transformed it into a trypanocidal substance which they termed ' trypanotoxyl '. . . . Yamanouchi (1910) considered that the trypanocidal substance was produced by the red cells ; he found that liver and other organs cleared of blood no longer possessed the power of activating atoxyl. Yamanouchi further observed that red cells acted more powerfully in the presence of carbon dioxide than under normal conditions, and that in the presence of oxygen they failed altogether to activate atoxyl ; pure recrystallized haemoglobin was without action. The active substance was soluble in alcohol, thermostable, and free from protein material. Terry (1912) found that both liver and blood, when incubated with atoxyl, transformed the drug into a toxic substance. The transforming agent in liver had, however, characteristics which, in some respects, were quite different from those of the active agent in blood. . . . In a later paper (1915), Terry showed that the toxic substance into which atoxyl is transformed (transformed atoxyl) is thermostable, but that the transforming agent in blood is thermolabile."

" We have concerned ourselves with a preliminary inquiry regarding the constituent of the red cell which is capable of increasing the trypanocidal power of pentavalent arsenicals.

" Our experiments showed that a solution of laked red cells was also able to activate tryparsamide in a similar degree to intact red cells. The extent to which a solution of red cells can activate tryparsamide is exceedingly great, as is shown by the following observation. The trypanocidal titre of a 1 per cent. solution of tryparsamide in ' medium,' either freshly-made or kept for 6 hours at 37°C., is 8 ; the trypanocidal titre of a 1 per cent solution of tryparsamide in a 12·5 per cent. solution of red cells which has been kept for 6 hours at 37°C. is about 16,000 ; thus, by substituting the red cell solution for ' medium,' the trypanocidal titre is increased no less than 2,000 times.

" We do not know what constituent of the blood is responsible for producing this change. It cannot be haemoglobin itself since solutions prepared from pure crystalline haemoglobin showed no power to activate tryparsamide ; and, furthermore, no differences were observed whether the haemoglobin was in the form of oxyhaemoglobin, reduced haemoglobin or carboxyhaemoglobin.

" Whatever its nature, the activating substance is relatively thermostable in that it resists almost completely a temperature of 65°C. for 30 minutes, and is not completely destroyed by a temperature of 75°C. for 30 minutes. The activating power of red cell solutions kept at 0°C. is gradually lost, so that, within two months or less, such solutions have become practically inert." *A. G. B.*

STRANGEWAYS (Winifred I.). **Trypanocidal Action of Two Arsenicals, K. 324 and K. 352, on Infections in Mice and Rabbits.**—*Ann. Trop. Med. & Parasit.* 1935. July 17. Vol. 29. No. 2. pp. 231–254.

This paper describes the trypanocidal action of two new aromatic arsenical compounds prepared by Dr. KING. The compounds are :—

K. 324. Di (β-carboxy-β-aminoethyl) benzamide-p-thioarsinite and K. 352. Di glutathionyl-4-acetamino-2-hydroxyphenyl thioarsinite. The tests were carried out on various trypanosomal infections in mice and rabbits. In order to control the investigation, parallel tests were made with tryparsamide.

Toxicity tests on mice were made with single intravenous injections. The mice were kept under observation for one month after treatment. It was found that the maximum dose which could be given to mice in a single intravenous injection was 0·075 mgm. per gm. of K. 324; 0·2 mgm. per gm. of K. 352; and 3·0 to 3·5 mgm. per gm. of tryparsamide.

The therapeutic values of the two drugs were tested on infections produced in mice by 5 different species of trypanosomes: (*a*) rapidly fatal infections due to *T. equiperdum*, *T. rhodesiense* and *T. brucei*, and (*b*) chronic infections due to *T. gambiense* and *T. congolense*. The results obtained with the acute infections are summarized in the following table which gives the approximate dose of each compound which produced 80 per cent. or more of cures, and also the therapeutic index, *i.e.*, the ratio of the minimum curative dose (M.C.D.) to the maximum tolerated dose.

Drug	*T. equiperdum* M.C.D. (mgm. per gm.)	*T. rhodesiense* M.C.D. (mgm. per gm.)	*T. brucei* M.C.D. (mgm. per gm.)
K. 324	0·015–0·025 (1 = 1/3·75)	0·01 (1 = 1/7·5)	0·0075 (1 = 1/10)
K. 352	0·02 (1 = 1/10)	0·01 (1 = 1/20)	0·01 (1 = 1/20)

It is clear from this table that the two compounds provide an efficient means of curing the 3 infections in mice. The strain of *T. brucei* was most easily cured, that of *T. rhodesiense* rather less so, while *T. equiperdum* required relatively large doses.

The strain of *T. gambiense* used in these experiments was obtained from a patient in Entebbe in 1931. Its virulence for mice varied a good deal, some animals dying within the comparatively short period of a month, whereas others lived for as long as 8 or 9 months without showing any signs of infection after the first week. At first these mice were discarded as spontaneous cures, but more recently this was found to be a false assumption, and it now seems probable that the choroid plexus is a seat of *T. gambiense* in mice, and that animals can harbour the trypanosomes here without showing any signs of disease. In view of the chronic character of the untreated infections, it was necessary to keep the experimental mice under observation for as long as possible. It was found that doses of 0·01 mgm. per gm. of either K. 324 or K. 352, and 0·75 mgm. per gm. of tryparsamide sufficed to clear the peripheral blood of *T. gambiense* infections for long periods. Relapses were common after treatment with half the above dose of either K. 324 and K. 352. As might be expected neither drug had any curative action on *T. congolense* infections in mice.

A long series of therapeutic experiments were undertaken on rabbits infected with the strain of *T. rhodesiense*. The drugs were given intravenously 20 to 25 days after the inoculation of trypanosomes. At this time there were pronounced oedematous lesions of the ears and eye-lids as well as of the external genitalia, and trypanosomes could readily be found either in the peripheral circulation or in the fluid from the lesions. Results are given of two types of treatment with each drug, viz.: single injections of small or large doses, and repeated injections of small doses. It was found that single doses of K. 324 up to 0·02 gm. per kilo can be administered with safety to rabbits infected with *T. rhodesiense*, and that permanent cures can be produced with doses of 0·015 and 0·02 gm. per kilo. Short courses of treatment consisting of 3 to 6 doses of 0·01 gm. per kilo. produced permanent cures in rabbits infected with *T. rhodesiense*, and longer courses of treatment with the same dose produced no toxic symptoms in normal rabbits.

Single doses of K. 352 up to 0·04 gm. per kilo. could be safely administered to rabbits infected with *T. rhodesiense*, and permanent cures were produced by 0·02 to 0·04 gm. per kilo. Short courses of treatment with 4 to 8 doses of 0·01 gm. per kilo. of K. 352 produced permanent cures, whilst longer courses of treatment with the same drug produced no toxic symptoms in normal rabbits.

The following summary is given :—

"1. The two aromatic thioarsinites K. 324 and K. 352 are effective in curing *T. equiperdum*, *T. rhodesiense*, *T. brucei* and *T. gambiense* infections in mice in doses which are only a fraction of the maximum tolerated.

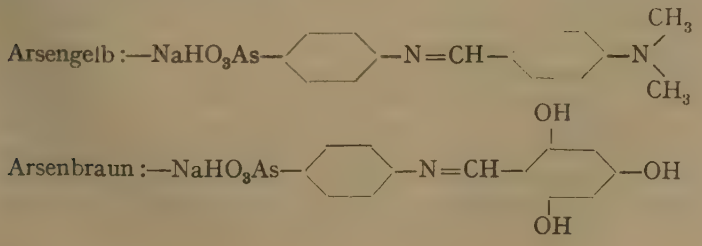
"2. Neither compound has any effect on *T. congolense* infections in mice.

"3. Rabbits infected with *T. rhodesiense* can be cured with single intravenous doses of both compounds, but more effectively by a short course of 3 to 8 smaller doses.

"4. The relatively small amount of arsenic required to effect permanent cures in rabbits infected with *T. rhodesiense* when administered as the two thioarsinites, compared with that required when given as an arsonic acid such as tryparsamide, is discussed." *W. Y.*

Fischl (Viktor) & Singer (Ernst). Chemotherapeutische Prüfung zweier arsenhaltiger Farbstoffe. [**The Chemotherapeutic Examination of Two Arsenic-containing Dyes.**]—*Biochem. Ztschr.* 1935. Feb. 22. Vol. 276. No. 4. pp. 277–279. [10 refs.]

The action of two arsenic containing dyes was tested on mice infected with nagana and *Sp. recurrentis*, respectively. The dyes in question are referred to as "Arsengelb" and "Arsenbraun"; they have the following formulae :—



It was found that both, especially the "Arsenbraun," were active on the trypanosome infection, and that "Arsenbraun" was also active on the spirochaete infection. *W. Y.*

Fischl (Viktor). Chemotherapeutische Prüfung einiger Pyrrolfarbstoffe. [**Chemotherapeutic Examination of Some Pyrrol Dyes.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1935. May 29. Vol. 85. No. 1/2. pp. 77–80. [10 refs.]

Wrede and Hettche have recently obtained from cultures of *Bacillus prodigiosus* a red dye, Prodigiosin, and Fischl has examined the therapeutic value of the perchlorate of this substance. He found that a suspension in almond oil given subcutaneously to mice infected with nagana caused the temporary disappearance of the trypanosomes. Three other pyrrol dyes—pyrrolblue, pyrrolred, and phtalocyanin—had no trypanocidal action. *W. Y.*

v. Jancsó (N.) & v. Jancsó (H.). Chemotherapeutische Mittel mit opsoninartiger Wirkung. [**Chemotherapeutic Drugs with an Opsonic Action.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1935. Apr. 29. Vol. 84. No. 5/6. pp. 471–504. With 1 fig. [16 refs.]

The authors discuss in detail their investigations on the opsonic action of certain drugs. As they have recorded in various earlier papers [*ante*, pp. 22 and 358] they have observed that the intravenous injection of an electro-colloidal copper preparation, in combination with splenectomy, completely prevents the phagocytosis of foreign particles or micro-organisms from the circulation, owing to an efficient elimination of the reticulo-endothelial system. This new technique has shown that phagocytosis and opsonic action plays just as important a part in chemotherapy as in immunology.

When animals experimentally infected with trypanosomes are treated with germanin the reticulo-endothelial cells of the liver, spleen and bone-marrow exhibit an enormous phagocytosis of flagellates, and this is dependent upon the opsonizing action of the drug. In other experiments trypanosomes were subjected to the action of germanin *in vitro*, and then equal numbers were injected into mice with an intact reticulo-endothelial system, and into mice which had been splenectomized and treated with electro-colloidal copper. In this way it was shown that the cells of the reticulo-endothelial system were able to phagocytose and destroy millions of living trypanosomes.

The preparation of trypanosomes for phagocytosis was not brought about only by germanin, but also by withdrawal of sugar. When trypanosomes suspended in a nutrient medium have exhausted the glucose content of the medium they become motionless, and in this condition of "sugar hunger" they are avirulent and become a ready prey to the reticulo-endothelium by which they are phagocytosed and destroyed. The addition of fresh serum or glucose, however, restores the virulence of the parasites. If trypanosomes in a condition of "sugar hunger" are injected intravenously into a normal mouse they are phagocytosed by the reticulo-endothelial cells to the extent of many millions within a few minutes. Experimental investigations have suggested that the basis of the action of germanin is a toxic

inhibition of the sugar metabolism of the trypanosomes, and consequently it is possible that the opsonic effect of the drug depends upon this action. This hypothesis is in harmony with the fact that trypanosomes obtained from an animal which has been given a dose of germanin consume less oxygen and sugar than do trypanosomes from an untreated animal.

The very interesting fact was discovered that whereas a normal strain of *T. brucei* when suspended in a solution of germanin for 30 minutes at 37°C. failed to bind the drug, nevertheless its trypaflavin-fast branch completely lost its virulence after similar treatment. It appears therefore that systematic treatment of a trypanosome strain with trypaflavin increases the permeability of the trypanosomes for germanin. This observation explains the synergism between trypaflavin and germanin. *W. Y.*

Singer (Ernst) & Fischl (Viktor). Arzneifestigkeit und Chemikaleingewöhnung der Trypanosomen. [**Drug-Resistance and Chemical Habituation of Trypanosomes.**]—*Zischr. f. Hyg. u. Infektionskr.* 1935. Feb. 25. Vol. 116. No. 6. pp. 683–687.

In previous papers the authors have put forward the view that although absorption of a drug by the parasite is necessary for chemotherapeutic action, it is not necessarily identical with this. They have shown that such drugs as atebrin and rivanol, which have no trypanocidal action, are just as readily absorbed by trypanosomes as is the trypanocidal dye trypaflavine.

It has now been established that when trypanosomes are exposed for some time to the action of trypanocidal substances, such as trypaflavine, a state of affairs is gradually reached in which the parasites no longer absorb the drug. It occurred to the authors that it would be interesting to ascertain what happened when trypanosomes were repeatedly exposed to the action of such non-trypanocidal substances as atebrin and rivanol. In striking contrast to what happens in the case of trypaflavine, it was found that trypanosomes, which had been subject to the action of the non-trypanocidal compounds during 12 passages through mice, instead of absorbing less of these dyes than the normal strain were capable of absorbing $2\frac{1}{2}$ times as much.

From this work it is concluded that chemical habituation is fundamentally different from drug-resistance. Systematic treatment of *T. lewisi*, which possesses a natural resistance to arsenicals, with solu-salvarsan, failed to influence the capacity of the trypanosomes to absorb the drug in either a positive or a negative direction.

W. Y.

von Jancsó (Nikolaus) & von Jancsó (Hertha). **The Rôle of the Natural Defence Forces in the Evolution of the Drug-Resistance of Trypanosomes. II.—The Rapid Production of Germanin-fast *T. brucei* Strains in Animals with Paralyzed Defence.**—*Ann. Trop. Med. & Parasit.* 1935. Apr. 25. Vol. 29. No. 1. pp. 95–109. With 1 fig. [21 refs.]

A description is given of a rapid method of producing germanin-fast strains of trypanosomes. The method consists essentially in eliminating the reticulo-endothelial system in mice, firstly by splenectomy 2 to 4 hours before treatment, and secondly by the intravenous injection of electro-colloidal copper 3 to 4 hours after the injection of germanin.

It was found that when mice infected with *T. brucei* were treated in this manner, a drug-fast strain of trypanosomes was obtained with remarkable rapidity. After 12 treatments in the " blocked " animals the trypanosomes were found to withstand the " dosis bene tolerata," *i.e.*, 1/200 gm. of germanin per 20 gm. mouse. This is in striking contrast with the attempts to produce a germanin-fast strain in the ordinary way.

The reviewer and his colleagues record that 12 months were required to make a strain of *T. rhodesiense* completely resistant to germanin ; and Leupold, who worked with the same strain as von Jancsó, records that maximal resistance to germanin was not obtained until after 100 passages.

von Jancsó considers that the most plausible explanation of this interesting phenomenon is that trypanosomes possess a capacity for adapting themselves very quickly to germanin, and that normally a rapid production of drug-fastness does not take place because the defence forces of the host (that is the reticulo-endothelial system) counteract the tendency to its production. *W. Y.*

von Jancsó (N.) & von Jancsó (H.). Chemotherapeutische Schnellfestigung von Trypanosomen durch Ausschaltung der natürlichen Abwehrkräfte. [**Rapid Production of Drug-fast Strains through Elimination of the Natural Defence Mechanism.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1935. May 29. Vol. 85. No. 1/2. pp. 81–105. With 1 fig. [27 refs.]

Reference is made to the rapid production of germanin-resistant trypanosomes by the treatment of infected mice in which the reticulo-endothelial system is eliminated by splenectomy and intravenous injection of electro-colloidal copper. This experimental work has already been published elsewhere and noticed in this *Bulletin* [*ante*, p. 22 and p. 358]. [The paper is of a highly technical nature dealing with various problems on the subject of drug-resistance ; it should be consulted in the original by those interested.] *W. Y.*

Schlossberger (H.) & Schüffner (R.). Festigungsversuche an Trypanosomen mit Arsenpyridinderivaten. [**Experiments on Resistance in Trypanosomes with Arseno-Pyridine Derivatives.**]—Reprinted from *Angewandte Chemie.* 1934. Vol. 47. p. 768 in *Arb. a. d. Reichsgsndhtsamt.* 1935. Feb. Vol. 67. No. 4. pp. 577–584. [19 refs.]

Experiments were devised with the object of ascertaining whether trypanocidal arsenical derivatives of heterocyclic compounds, particularly of pyridine, are capable of a therapeutic effect upon trypanosomes rendered resistant to a phenylarsonic acid preparation, and whether trypanosomes resistant to an arsenopyridine compound can be influenced by a phenylarsonic preparation.

The experiments were made on *T. brucei* infections in mice. Two resistant varieties of the strain, viz.: one resistant to tryparsamide, and the other to the preparation BRI (*i.e.*, mono-sodium salt of 2-pyridone 5-arsonic acid) were prepared in the usual way. The minimum therapeutic dose of each of a large number of preparations was determined on infections produced by the normal and by the two resistant strains. The preparations used included tryparsamide

and BR1, a number of arsenopyridine compounds, viz.: BR20, BR23, BR120, BR121, and also arsenophenylglycine, an arsenostibinobenzene derivative (Sdt 355), trypaflavine, germanin, tartar emetic and fuadin. The results of the experiments are given in detail in tabular form. They show that the strain made resistant to the arsenopyridine compound, BR1, was resistant not only to the other arsenopyridine derivatives, but also to tryparsamide, trypaflavine and fuadin. The tryparsamide-resistant strain, however, proved sensitive to BR1, and particularly so to BR23 and to fuadin.

These observations can be explained only on the assumption that the mechanism of action of both pyridine derivatives (BR1 and BR23) differs from that of tryparsamide and from that of the phenylarsonic derivatives. These results resemble those of EHRLICH in the course of his investigations on drug-resistance whilst studying arsenophenylglycine, results later confirmed by the reviewer and his colleagues.

The conclusion seems justified that, similarly to arsenophenylglycine, the arsenopyridine preparations BR1 and BR23 possess affinities to the protoplasm of the trypanosomes which tryparsamide and other derivatives of phenylarsonic acid do not have. Since, however, the BR1-resistant strain can be appreciably affected by arsenophenylglycine, the anchoring points of arseno-pyridine compounds must partly differ from those of arsenophenylglycine. In terms of EHRLICH's chemoceptor theory, it would appear that the two arseno-pyridines possess "secondary haptophors," just as does arsenophenylglycine, but that they are different from those of arsenophenylglycine. From the practical point of view, these conclusions are important, because they indicate possibilities of cure in cases where organisms resistant to tryparsamide, atoxyl, etc., are involved. *W. Y.*

BROWNING (C. H.) & GULBRANSEN (R.). **Variation in Chemotherapeutic Susceptibility associated with Change in Virulence of a Strain of** *Trypanosoma brucei*.—*Jl. Hygiene.* 1935. May. Vol. 35. No. 2. pp. 180–184.

A strain of *T. brucei* when first introduced into mice produced infections relatively resistant to various drugs, but when the strain had become highly accommodated, and its pathogenicity increased to a maximum as the result of repeated passages, the infected mice were readily cured.

The strain of *T. brucei* used in these experiments was obtained by ADAMS from a dog which had been exposed to the bites of wild fly in Uganda. It was preserved by passage through six guineapigs during the course of 8 months, and thereafter maintained by passage through mice. Up to the 12th passage most of the mice showed a marked fluctuation in the number of parasites in the blood before death finally took place when they were numerous. This fluctuation, as well as the length of survival, are better indications of the state of accommodation of the trypanosomes than is the incubation period. From the 14th passage onwards the strain possessed nearly the maximal pathogenicity, and the parasites appearing in the blood increased progressively until death, which in all animals, except one in the 18th passage, occurred within 3 days thereafter. The strain, therefore, accommodated itself fairly rapidly to the mouse.

Therapeutic tests with various trypanocidal substances were carried out during the early passages (1 to 8) and also during later passages

(34 to 290). The results, which are summarized in a table, showed that the infection at first was markedly resistant to all the substances tested, viz.: arsacetin, tryparsamide, trypanblue, Bayer 205, trypaflavine, and styryl-quinoline compounds. Animals of the later passages were, however, for the most part cured by the same or smaller doses of these drugs.

The exact mechanism on which this difference depends was not investigated, but attention is drawn to the interesting fact that chemotherapeutic response was weak at the time when the host itself was able to exercise an effective resistance, and that later, when the host's resistance had become negligible, the curative action of the drugs was pronounced. *W. Y.*

Browning (C. H.) & Gulbransen (R.). **Combined Treatment of Experimental Trypanosome Infections by Chemotherapeutic Agents.** —*Jl. Path. & Bact.* 1935. May. Vol. 40. No. 3. pp. 425–431. [25 refs.]

Experiments showed that combined therapy in which tryparsamide and styryl-245 were used in sequence produced a greater curative effect in mice infected with *T. brucei* than followed the use of large doses of either substance alone.

The results of the experiments are set out in a series of tables. It was found that of the mice treated with tryparsamide alone, all those which were given a dose of 1 : 400 or less relapsed, as did one of the two mice which received a dose of 1 : 150. In the case of treatment with styryl-245 alone considerable variation in action was seen, thus 1 : 2,000 did not invariably lead to cure, whilst 1 : 24,000 produced cure in a few cases. With doses of 1 : 2,000 to 1 : 5,000, 10 of 23 animals were cured, whilst with doses of 1 : 20,000 to 1 : 30,000 only one of 23 mice was cured.

Where tryparsamide and styryl-245 were used jointly, 1 : 250 to 1 : 400 of the arsenical and 1 : 7,500 to 1 : 18,000 of the styryl compound produced a cure in all of 17 animals; whilst tryparsamide 1 : 400 with 1 : 24,000 to 1 : 30,000 of styryl cured 17 of 33 mice.

The authors believe that the evidence is strongly in favour of this result being more than a mere summation of effects. It is left undecided how exactly this "potentation" or "synergic" action is produced, but it is emphasized that tryparsamide is quickly absorbed and excreted, whereas the styryl compound is slowly absorbed and acts gradually. The advantage of combined treatment in this particular instance may be due to the prolonged influence of the styryl compound on parasites weakened by the arsenic, as well as to the fact that the substances differ widely in chemical constitution and so are likely to attack the parasites at different points. *W. Y.*

i. Hassko (A.). Experimentelle Beiträge zur Wirkungsweise chemotherapeutischer Mittel I. [**The Mode of Action of Chemotherapeutic Substances.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1935. Feb. 25. Vol. 116. No. 6. pp. 660–668. [11 refs.]

ii. ——. Untersuchungen ueber den Wirkungsantagonismus chemotherapeutischer Mittel II. [**The Antagonistic Action of Chemotherapeutic Substances.**]—*Ibid.* pp. 669–671.

i. The experiments described in this paper were devised with the object of ascertaining something about the mechanism of action of

certain drugs, *e.g.*, parafuchsin, trypaflavine and neosalvarsan, on trypanosomes, and especially whether their action was direct.

Rats were inoculated with a strain of nagana very sensitive to trypaflavine and salvarsan, and at the height of the infection were treated with one or other of the three drugs in question. At various intervals afterwards the animals were killed by bleeding and the trypanosomes separated from the cellular elements of the blood by fractional centrifugation. The amount of dyestuff bound by the trypanosomes was estimated colorimetrically and the amount of neosalvarsan by chemical reagents. At various times after treatment the vitality of the parasites and their virulence were examined by subinoculation into mice.

It was found that when trypanosomes which had been treated with trypaflavine or neosalvarsan were subinoculated into normal mice multiplication of the parasites was delayed. Their infectivity was proportional to the dose and the therapeutic index of the drug, and to the time of its action. Trypanosomes treated with parafuchsin were just as infective for normal mice as was the normal untreated strain. In tables the authors show the amount of parafuchsin or trypaflavine found in the trypanosomes at various intervals after treatment of infected rats. Parafuchsin showed less avidity for the parasites than did acriflavine ; it was found that the trypanosomes took up 10 times as much acriflavine as parafuchsin.

Neosalvarsan itself, however, could not be demonstrated in the trypanosome body. The authors therefore believe that the active agent must be formed by the body of the host from neosalvarsan and that this product, whatever it may be, acts directly on the parasites.

In further experiments it was noticed that blocking of the reticulo-endothelial system limited the action of tartar emetic, and the conclusion is reached that the function of this system is to remove damaged parasites by phagocytosis.

ii. Previous experiments had suggested that dyes belonging to the triphenylmethane series behave differently in trypanosome infections of rats and mice. For example, it is stated that brilliant green given to a nagana infected rat greatly interferes with the effectiveness of a subsequent dose of acriflavine, but that this does not happen with the same infection in white mice ; and conversely previous treatment of infected rats with methyl- or ethyl-violet scarcely interferes with the action of acriflavine, but in mice exerts a definite antagonistic action.

The author determined to re-investigate these questions. A number of experiments were performed with white rats infected with a strain of nagana sensitive to the triphenylmethane dyes. The animals were given 5 mgm. per 100 gm. of either methyl violet, ethyl violet or pyoktanin, or 10 mgm. per 50 gm. of trypanrot or trypanblue. An hour later they were given subcutaneously 1 mgm. per 50 gm. of trypaflavine. After the lapse of a further hour the rats were killed by bleeding, the trypanosomes separated from the cellular elements of the blood, dried and weighed, and their content of dye or acriflavine determined. It was found that a preliminary dose of methyl violet, ethyl violet or pyoktanin greatly lessened the capacity of the trypanosomes to take up acriflavine, whilst the preliminary dose of trypanrot or trypanblue almost entirely prevented the absorption of acriflavine by the parasites. *W. Y.*

Launoy (L.). De l'action synergique de l'arsenic et de l'antimoine dans le traitement du nagana expérimental de la souris. [**Synergic Action of Arsenic and Antimony in the Treatment of Experimental Nagana in Mice.**]—*Bull. Soc. Path. Exot.* 1935. Apr. 10. Vol. 28. No. 4. pp. 324–329.

It is well known that nagana in mice is very sensitive to arsenical compounds and to Bayer 205, but relatively resistant to antimony compounds. The author has asked himself whether it is possible to obtain any synergic action with a very active arsenical compound and a relatively inactive antimonial compound.

For his experimental work he selected orsanine as his arsenical preparation, and two compounds of antimony, viz.: antimony trithiosalicylate of sodium and antimony III-thiomalate of lithium. It was found that a dose of 3 mgm. of orsanine intravenously cured 100 per cent. of infected mice. The doses used in the synergic experiments were (*a*) Orsanine 1 mgm. and Sb. trithiosalicylate of sodium 0·5 mgm.; and (*b*) Orsanine 1 mgm. and Sb. thiomalate of lithium 1·4 mgm. to 1·8 mgm. It was found that this dose of orsanine alone cured only about 23 per cent. of animals. Of 35 mice treated with 0·5 mgm. of the first antimony compound, none were cured. Of 30 mice treated with 2·8 mgm. of the second antimony compound, 16 were sterilized and some died from poisoning. With the lower dose mentioned above only a few animals were sterilized. The results of the synergic experiments are as follows:—

The first pair of drugs given simultaneously in the doses mentioned cured 5 of 10 mice, and when given successively they cured 3 of 10. The second pair of drugs gave better results. When the dose of the antimony compound was 1·4 mgm. 7 of 10 mice were cured, and when the dose was 1·8 mgm. all the mice were cured. *W. Y.*

Duke (H. Lyndhurst). **Arsenic Resistance in Trypanosomes.** [Correspondence.]—*Lancet.* 1935. Apr. 13. pp. 903–904.

Duke complains that the reviewer and his colleague, Dr. Murgatroyd, in their recent Address to the Royal Society of Tropical Medicine on the subject of chemotherapy, omitted to refer to certain experiments performed by him in Uganda. [It was, of course, impossible, in the limited period available, to summarize the entire literature of chemotherapy, and reference was made to a few only of those articles which seemed to the reviewer and his colleagues to bear most directly on the various points discussed.] *W. Y.*

Fischl (Viktor) & Singer (Ernst). Die Chemotherapie der Rattentrypanose. [**The Chemotherapy of Rat Trypanosomiasis.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1935. Feb. 25. Vol. 116. No. 6. pp. 652–659. [43 refs.]

This work was undertaken with the object of throwing light on the mechanism of the action of chemotherapeutic substances on infections due to *Trypanosoma lewisi*.

Apart from arsenophenylglycin the only substances known to have any action on *T. lewisi* infections are BR23, Sdt. 355 and 386B (Christison) and, to a slight degree, atoxyl. The authors themselves have tried the effect of sodium arsenite, m-amino-p-oxyphenyl sodium arsenite, sodium salvarsan, solusalvarsan, sulfoharnstoff, ruthenrot, rhodium sodium chloride, trypaflavine and human serum. All these substances were found to be inactive. In a couple of tables are collected

the results obtained by various workers, and by the authors themselves, with these and many other substances on *T. lewisi* and related apathogenic trypanosomes.

In addition to its action on *T. lewisi* arsenophenylglycin exhibits another peculiarity, namely, that it can affect pathogenic trypanosomes which have been made resistant to other arsenicals; this property EHRLICH called "avidity." CHRISTISON explained this phenomenon on EHRLICH'S hypothesis as follows:—Although *T. lewisi* and arsenic-fast nagana trypanosomes possess no arseno-receptors, they are provided with an acetico-receptor which is capable of anchoring arsenophenylglycin to their cytoplasm. The negative results of Christison with BR68, and of the authors with solusalvarsan, and the positive results of Christison with atoxyl, BR23 and Sdt. 386B show, however, that the acetic acid ester alone cannot explain the action on the apathogenic trypanosomes. It is still more difficult to explain on chemical constitution the activity of drugs on *T. lewisi* and arsenic-fast strains of pathogenic trypanosomes, respectively.

In order to throw light on the mechanism of action of chemotherapeutic substances on *T. lewisi*, the authors injected a series of rats in an early stage of infection with various substances, *e.g.*, arsenophenylglycin, atoxyl, sodium salvarsan, neosalvarsan, solusalvarsan, sodium arsenite, solganol and sulfoharnstoff. The animals were killed an hour later by bleeding and the amount of arsenic or gold determined in the plasma, red corpuscles and trypanosomes, respectively; the arsenic was estimated colorimetrically and the gold by a spectrographic method. The results are set out in a table from which it appears that trypanocidal action and anchoring of the drug are parallel; the active arsenophenylglycin is absorbed by the trypanosomes in considerable amount, whilst the slightly active atoxyl is absorbed in much smaller amount. The remaining inactive arsenicals were absorbed in very small amounts. The gold compounds—solganol and sulfoharnstoff—were, however, absorbed in considerable quantities notwithstanding their complete therapeutic inactivity.

These results show once more that absorption of a drug is not necessarily identical with curative effect; although absorption of a certain quantity of the drug is necessary for curative effect, the converse is not true; a considerable quantity of a drug can be absorbed without curative action. *W. Y.*

CORSON (J. F.). **A High Rate of Salivary Gland Infection of** *Glossina morsitans* **with** *Trypanosoma rhodesiense*.—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935. Mar. 8. Vol. 28. No. 5. pp. 501–504.

After referring to the fact that in transmission experiments with *G. morsitans* and *T. rhodesiense* it is usual to obtain less than 10 per cent. of salivary gland infections, the author gives details of an experiment in which a very high proportion of such infections was obtained.

A reedbuck was bought in the sleeping sickness area of the Kahama District of Tanganyika in September, 1934. In 1928–1929 it was estimated by MACLEAN that the sleeping sickness in the particular district in which this reedbuck was caught amounted to the unusually high figure of 22 per cent. The reedbuck was taken to the Tinde Laboratory and remained in good health. Examinations of its blood and subinoculations into 9 white rats were negative. On Sept. 14th two isolated *G. morsitans* infected with *T. rhodesiense* were fed on the reedbuck.

The history of the strain is as follows :—

24.7.33. Man—Guineapig 95—Fly10—Dikdik 2—Fly K8—Dikdik 8—Fly S8—Dikdik 13—Fly AA53—Dikdik 19—Flies AL27 and 41—Reedbuck. 14.9.34.

This strain was shown in August, September and October, 1934, to be infective for man. In transmission experiments from infected dikdiks by *G. morsitans* usually one or two infective flies out of about 20 to 40 survivors were isolated. On October 4th about 120 laboratory-bred *G. morsitans* were fed on the reedbuck, the blood of which showed a scanty infection of trypanosomes ; the flies were again fed on Oct. 7th and another box of about 30 flies was added on this occasion. On this day only 3 trypanosomes were found during the examination of 3 thick films of the reedbuck's blood. The flies were then fed on a healthy sheep until Oct. 23rd, after which they were transferred to monkeys. When the monkeys became infected the 85 flies left were put singly into bottles, and each fly was allowed to bite a white rat ; 47 rats became infected. Further animals were infected, and finally the flies were dissected and 46 showed infected salivary glands ; including the flies which had infected rats, but which were not dissected, 51 (60 per cent.) of the 85 flies had infected salivary glands. The blood of the rats showed numerous posterior-nuclear forms, the incubation period was 45 days and the duration of life about 20 days. There was nothing unusual in the climatic conditions ; the temperature of the air of the laboratory ranged daily from about 70–85°F., sometimes reaching 90°F. The flies were kept in boxes over water in trays, partly to keep the air moist and partly to guard against white ants.

A similar experiment with the same strain of trypanosomes in a dikdik, and with flies from the same batches of pupae, ran concurrently with the reedbuck experiment ; in this, although the infection was transmitted to a monkey and 32 flies survived to feed singly on rats, an infective fly was not isolated.

In view of these remarkable results, it appeared desirable to repeat the experiment accompanied by some form of control. In the second experiment 120 *G. morsitans* were fed on the same reedbuck on the 9th and 12th November. On the 6th December, the surviving flies were dissected and 28 (33·3 per cent.) of the 84 surviving flies were found to have infected salivary glands.

In the control experiment a few of the isolated flies infected in the original experiment were allowed to bite a monkey on the 8th November. This monkey became infected and 120 *G. morsitans* were fed on it on the 13th, 14th and 15th November. The rate of infection of the salivary glands in this experiment was only 1·1 per cent. In Corson's opinion the special suitability of the reedbuck's blood rather than a selective change in the trypanosomes appears to be the most likely explanation of this interesting observation. *W. Y.*

Corson (J. F.). **Further Observations on Francolin and Guinea-Fowl as Reservoirs of** *Trypanosoma rhodesiense*.—*Jl. Trop. Med. & Hyg.* 1935. Feb. 15. Vol. 38. No. 4. pp. 46–47.

In previous papers it was shown that francolin and guinea-fowl were susceptible to infection with *T. rhodesiense* [this *Bulletin*, Vol. 29, p. 635]. In his present work Corson has firstly attempted to infect these birds by allowing isolated infected *G. morsitans* to feed upon them, and secondly he has endeavoured to ascertain whether guinea-fowl in an evacuated sleeping sickness area are infected by inoculation of their blood into rats.

In the first portion of his work Corson used a strain of *T. rhodesiense* isolated from man in July, 1933, and since maintained by passage through *G. morsitans* and dik-diks. A bottle containing the infected fly was applied to the leg of the bird until the fly bit or fed. Rats were subsequently inoculated from the birds and laboratory-bred flies fed on those birds which had been shown to be infected. Details of the successful experiments are given in a table. Three of the 19 francolin and 3 of the 9 guinea-fowl became infective to rats. One francolin remained infective for 3 months and 1 guineapig for 18 days, but not for 2 months. Several hundred laboratory-bred *G. morsitans* were fed on the infected birds, but the infection was not transmitted.

The second group of experiments was performed at Mkwemi in the Kahama district. The population had been evacuated in 1928, because of sleeping sickness. Tsetse and antelope are plentiful. In all, 134 rats were inoculated from 67 guinea-fowl, but none became infected.

Corson concludes from this and his previous work that francolins and guinea-fowl, like the domestic fowl, need not be considered as more than, at most, very rare and temporary reservoirs of *T. rhodesiense*.

W. Y.

Packchanian (Ardzroony). **A Method of maintaining Laboratory Strains of *Trypanosoma brucei* in a Subspecies of *Peromyscus maniculatus*.**—*Jl. Lab. & Clin. Med.* 1935. Feb. Vol. 20. No. 5. pp. 510–515. With 2 charts. [11 refs.]

The author suggests the use of an American deer mouse, viz. : a sub-species of *Peromyscus maniculatus*, as a suitable laboratory animal for maintaining parasitic strains of *T. brucei*, *T. equiperdum* and *T. evansi*. In comparison with the procedure usually adopted of maintaining these trypanosomes in rats, mice and guineapigs, the method recommended is both inexpensive and time-saving.

When *P. maniculatus* is inoculated intraperitoneally with *T. brucei*, the parasites appear in the circulation in 2 or 3 days ; they gradually increase until they are very numerous, and then they more or less suddenly disappear from the circulation. The first crisis and the subsequent short latent period are followed by a relapse, the parasites steadily increasing in number until they are swarming. Occasionally the animal dies at this stage, but more commonly there is a series of crises and relapses.

In the author's experiments, it was found that the minimum period of life of *P. maniculatus* infected with the laboratory strains of *T. brucei* and *T. evansi* was 21 days, the maximum period was 230 days, and the average about 80 days. There was no evidence that the sojourn of the parasites in this host caused any attenuation in their pathogenicity for ordinary laboratory animals.

W. Y.

van den Branden (F.). Pouvoir infectant du sang de rats albinos, après injection sous-cutanée massive de *Trypanosoma congolense* et de *Trypanosoma brucei*. [**Infectivity of the Blood of Albino Rats after Massive Subcutaneous Injection of *T. congolense* and *T. brucei*.**]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 14. pp. 1479–1481.

The author objects to the modification of the term " incubation " suggested by Valenza (1934–35), who distinguishes between what he calls bacteriological incubation and clinical incubation.

He performed a series of experiments in which rats were inoculated subcutaneously with *T. congolense* or *T. brucei*. These strains were both very virulent, killing the rats in 6 to 8 days, the trypanosomes appearing in the blood in 4 or 5 days. An albino rat weighing 100 to 120 gm. was then given subcutaneously 1 cc. of blood rich in trypanosomes: an hour later the heart was punctured and 1 cc. of blood removed added to 0·25 cc. of 6 per cent. citrate solution and injected subcutaneously into a healthy rat. This animal showed trypanosomes in its blood 4 to 5 days after the inoculation. Blood removed from the heart of the first rat 36 to 48 hours after infection was likewise infective for healthy rats, but the incubation period was prolonged for a couple of days. From this it is concluded that after a massive injection of trypanosomes the parasites are soon found in the circulation in considerable numbers, but later on (between the 36th and 48th hours) they are caught up in the deep organs; and finally they overflow into the blood. This experiment was repeated many times, both with *T. congolense* and *T. brucei*, and the results were always the same. In conclusion van den Branden writes that it is very desirable, in medicine and in natural science, to avoid modification of common terms which are consecrated both by time and by tradition. *W. Y.*

VAN DEN BRANDEN (F.). Sur le rapport du poids de la rate ou du foie au poids du corps, chez des rats blancs (variété albinos de *Mus decumanus*), non infectés, ainsi que chez les animaux de même espèce, préalablement infectés de *Trypanosoma congolense* ou de *Trypanosoma brucei*, puis guéris ou non guéris par traitement. [**The Relationship of the Weights of the Spleen or of the Liver to the Weight of the Body in Normal White Rats and in those Infected with *T. congolense* or *T. brucei*, and Subsequently either Cured or Not Cured by Treatment.**]—*C. R. Soc. Biol.* 1935. Vol. 119. No. 20. pp. 529–530.

VALENZA, in a recent paper, has drawn attention to the considerable enlargement of the spleen in certain animals infected with *T. congolense*, and has inquired whether the weight of the spleen in treated mice would not provide useful indications concerning the course of the infection and proof of cure. He concluded from his work that hypertrophy or non-hypertrophy of the spleen was a satisfactory indication of cure or non-cure of treated animals. VALENZA used the formula PR/PC × 100, where PR represents the weight of the spleen and PC the weight of the body.

Van den Branden has repeated this work, using white rats infected with *T. brucei* or *T. congolense*, and in addition has investigated the variation in the weight of the liver. In normal rats he found PR/PC × 100 varied between 0·4 and 0·6, whereas the formula PF/PC × 100 was on an average 5. In rats infected with *T. congolense* PR/PC × 100 varied between 1·0 and 3·0, and PF/PC × 100 averaged 5. In rats infected with *T. brucei* the figures were approximately the same.

The conclusion reached, therefore, is that the spleen is greatly hypertrophied in rats infected with *T. congolense* or *T. brucei*, whereas the weight of the liver remains normal. Histological examination of the hypertrophied spleen showed that the enlargement was due to a great increase in the reticulo-endothelial system.

In rats infected with *T. congolense* or *T. brucei*, and subsequently cured by a trivalent antimonial, the formulae were practically identical

with those given by normal animals ; whereas in rats unsuccessfully treated the formula PR/PC × 100 gave a value of 1·0 or more.

Van den Branden's work, therefore, confirms VALENZA's hypothesis, namely, that the presence or absence of splenic hypertrophy affords indication of cure or non-cure. *W. Y.*

VALENZA (J.). Maladies expérimentales de réinfection. [**Experimental Re-infection.**]—*Arch. Inst. Pasteur de Tunis.* 1935. Jan. Vol. 24. No. 1. pp. 92–98.

In his work on the therapy of *T. congolense*, the author found that a certain number of guineapigs infected with this parasite were cured either by moranyl alone or by this drug in combination with tryparsamide or with Sb-111-thiomalate of sodium. The object of the present experiment was to determine whether the animals thus cured were immune to a new infection with the same parasite.

The general conclusion to be drawn from this investigation is that the cured animals are not immune to re-infection ; but it was observed that in certain cases the second infection was manifested only by a rise of temperature, the blood remaining negative and not infecting a fresh animal. A second re-infection always succeeded, and this suggests that the first re-infection had exhausted the antibodies circulating in the blood. *W. Y.*

TSENG (Hsienli). Ueber die gegenseitige Beeinflussung verschiedener Trypanosomen bei Mischinfektion. [**On the Reciprocal Influence of Different Trypanosomes in Mixed Infections.**]—*Zent. f. Bakt.* I. Abt. Orig. 1935. June 14. Vol. 134. No. 3/4. pp. 153–159.

It has long been known that different species of bacteria may, in mixed infections, exert an antagonistic action on one another ; but little is known about the antagonistic action of different species of protozoa, and it was with the object of investigating this problem that the experiments described in the present paper were undertaken.

The author used young rats and mice, and species of trypanosomes which were morphologically easily distinguishable from one another, viz. : *T. congolense*, *T. gambiense* or *T. brucei*, *T. lewisi* and *T. cruzi*. In pure infections it was found that *T. gambiense*, *T. lewisi* and *T. cruzi* appeared in the blood in about 4 to 6 days, whilst *T. congolense* and *T. brucei* appeared within 1 or 2 days. Infections with the last two trypanosomes were rapidly fatal ; the other infections ran a chronic course.

Mixed infections with *T. gambiense*, *T. lewisi* and *T. cruzi* produced no definite result. Very different, however, was the case in another set of experiments in which the mixed infections consisted of *T. congolense*, *T. brucei* and *T. cruzi*. In this series of experiments, *T. brucei* completely inhibited the development not only of *T. cruzi*, but also of *T. congolense*. In order to investigate this interesting phenomenon more carefully, a number of rats were inoculated with *T. congolense*, and when this parasite was present in the blood 3 days later, the animals were also inoculated with *T. brucei*. The results, which are set forth in a table, show that the *congolense* infection waned as the *brucei* infection waxed. Somewhat similar results were obtained with mice, and the general conclusion drawn is that *T. brucei* infections are antagonistic to *T. congolense*. *W. Y.*

SCHILLING (Claus). Immunisierung gegen Trypanosomenkrankheiten. [**Immunization against Trypanosomiasis.**]—*Deut. Med. Woch.* 1935. May 24. Vol. 61. No. 21. pp. 832–834.

——. Immunization against Trypanosomiasis.—*Jl. Trop. Med. & Hyg.* 1935. May 1. Vol. 38. No. 9. pp. 106–108.

The author has continued in Tanganyika his work on immunization against trypanosomiasis [this *Bulletin*, Vol. 31, p. 213]. As mentioned in his earlier papers, it is essential that immunization is performed on quite young animals, and accordingly in the present work he has used young calves, since foals do not exist in the part of Africa in which he was working, *e.g.*, Tinde. Of the three species of trypanosomes found in Tanganyika, *T. congolense*, *T. brucei* and *T. vivax*, the last does not exist in Tinde. Schilling found it only once in the blood of a calf which had been infected by flies brought from Masumbwe, 77 miles away. In view of the scarcity of the spontaneous infection, and of the difficulty in getting sufficient quantities of the parasite, it was considered unnecessary to immunize against *T. vivax*. This, Schilling says, proved to be "a bad mistake."

When the inoculations and vaccinations were completed, the calves (and their mothers) were sent from Tinde to Masumbwe on June 25, 1934. This small village was chosen because previous attempts to keep cattle there had always ended in their destruction by nagana. Schilling had to leave Masumbwe in November, but the calves were left under the observation of a native Veterinary Assistant and under the control of HORNBY. Schilling has received notes on the behaviour of the animals up to January 31, 1935.

The first series was premunized by the minimal infection method, not more than 50 parasites being given in one dose. If trypanosomes did not appear in the blood of the inoculated animal within about a fortnight, and if the calf showed no signs of sickness and had increased in weight, the injection was repeated. Of the 23 calves treated in this way, 13 (57 per cent.) were alive after 7 months in tsetse areas, but for various reasons these figures required modification. For one reason or another Schilling eliminates 11 of the 23 animals and states that of the remaining 12 only one (9 per cent.) has died.

In the second group, a vaccine was used as antigen. Rats infected with *T. brucei* or *T. congolense* were killed when their blood was swarming with trypanosomes. The blood was defibrinated and dried in a shallow dish by fanning. Unfortunately, it was not found possible to keep the material sterile, so that after subcutaneous injection of the dark-brown emulsion (1 : 10 of sterile water) suppuration occurred in many cases. As a rule, 10 to 20 cc. of the above emulsion were injected. Of two calves which had been given one injection of vaccine only and had been bitten by infected flies 22 days later, one died 15 weeks and the other 36 weeks afterwards. Ten calves had 4 injections of vaccine at fortnightly intervals. Seven months later 9 were still alive.

A third group of five calves was exposed to infected flies, and when trypanosomes were found in the blood the calves were given half the curative dose of antimosan in two injections; 4 of the 5 animals are dead.

Of the 13 control calves, 8 (61 per cent.) are dead, and of the 31 cows not premunized 16 (51 per cent.) died within 7 months and all the rest were infected.

Schilling says that the number of his experiments is small, but the results obtained, viz. : 70 to 91 per cent. of the premunized animals alive, and only 39 per cent. of the non-premunized calves, suggest that there can be no doubt that the difference is a really significant one. He considers that the experiments should be continued and lays down certain rules for the guidance of those who may work on the subject in the future. It is emphasized that only calves which are thriving well should be used and that premunition must be performed against all three species of trypanosomes ; the rare *T. vivax* must not be neglected, as it sometimes produces quite deadly infections in cattle. At the present time it cannot be said definitely which of the two methods of premunition gives the better results. In favour of the minimal infection method is the simplicity of the technique ; this method is nearest to Nature's process, but a loss of 26 per cent. from the inoculation as was obtained in the present experiments is too high. Schilling believes that it can be lowered by more exact counting of the number of parasites injected. A very important matter is the proper choice of the season for the experiments, the time of reaction must coincide with the season of richest food supply, that is during the beginning of the rains.

A few experiments on pregnant cows indicate that there is a possibility that we can imitate the natural process of immunization of game still more closely by influencing the foetus *in utero* by a labile infection produced in the organism of the mother cow. *W. Y.*

Kligler (I. J.) & Comaroff (R.). **Susceptibility and Resistance to a Trypanosome Infection. IX.—Active Immunization of Rats and Guinea-pigs and Passive Immunization of Rats to a Trypanosome Infection.**—*Ann. Trop. Med. & Parasit.* 1935. July 17. Vol. 29. No. 2. pp. 145–160. [24 refs.]

The experiments described in this paper were devised with the object of studying the mechanism of resistance to trypanosome infections. On the one hand the authors attempted to ascertain whether immunity can be produced in rats, guineapigs and rabbits by repeated injections of dead trypanosomes ; and on the other hand they have studied the possibility of passive immunization of rats by the injection of the serum of guineapigs, rabbits and cats containing demonstrable trypanolytic antibodies.

Experiments are recorded in detail and the results summarized in tables. It was found that one or more injections of a suspension of dead trypanosomes (vaccine) increased the resistance of the rats to an infection with the same organism. The resistance produced by 20 injections was, however, not greater than that produced by 10 injections. Four rats out of more than 100 used in these experiments completely resisted infection ; 3 of these remained immune for a period of two months, after which they reacted in the same manner as the control animals. After repeated injections the blood of 2 of 10 rats tested contained demonstrable quantities of lytic antibodies.

The authors believe that the enhanced resistance in the rat produced by vaccination is due chiefly to an activation of the reticulo-endothelial system. They base this conclusion on the following observations :— (1) Injection of dead trypanosome suspensions increased the resistance of treated rats ; (2) injection of dead trypanosome suspensions mobilize

the large mononuclear cells in the peritoneal cavity ; and (3) the loss of the enhanced resistance following splenectomy.

It was found that the intravenous injection of the specific vaccine into rabbits resulted in the production of a specific lytic antibody. Lytic serum taken from infected guineapigs and cats, after a crisis, when injected into rats, prior to, or shortly after, inoculation with trypanosomes resulted in a retardation of the infection.

The general conclusion drawn by the authors from this work is that in the rat the enhanced immunity resulting from the injection of dead trypanosomes is due to an activation of the reticulo-endothelial system. *W. Y.*

Rodhain (J.) & Brutsaert (P.). L'évolution des *Trypanosoma lewisi* et *Trypanosoma cruzi* chez *Melophagus ovinus*. [**Development of** *T. lewisi* **and** *T. cruzi* **in** *Melophagus ovinus*.]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 12. pp. 1228–1231.

Experiments are described showing that *T. lewisi* and *T. cruzi* can develop in *Melophagus ovinus* with the appearance of metacyclic trypanosomes in the posterior part of the intestine.

The authors point out that the digenetic trypanosomes can be divided into two groups according to whether their development in the invertebrate host takes place in the anterior or posterior part of the intestine. The trypanosomes of the first group are inoculated by the bite of the infected insects (tsetse) and they are pathogenic to the vertebrate host. Those of the second group reach the vertebrate through the faeces of the invertebrate ; except for *T. cruzi* they are non-pathogenic, and they are also distinguished from the first group by the fact that they are readily cultured and by their perfect adaptation for the invertebrate host. In nature, as in the laboratory, a large proportion of the invertebrate hosts becomes infected, and furthermore many of them can be transmitted by a number of invertebrates. For example, *T. lewisi* can develop not only in *Ceratophyllus fasciatus*, the common rat flea, but also in *Xenopsylla cheopis* and in *Ctenopsylla musculi*, *Ct. canis*, and *Pulex irritans* ; and Brumpt has shown that it can also develop in the flea of the swallow, *Ceratophyllus hirundinis*. *T. cruzi* on the other hand develops in many species of reduviid bugs, in *Cimex lectularius*, *C. rotundatus* and *C. boueti*, and also in certain ticks, *e.g.*, *Ornithodorus moubata* and *Rhipicephalus sanguineus*.

A number of experiments were conducted to see whether these two trypanosomes would develop in *Melophagus ovinus*. The arthropods obtained from pupae were placed on guineapigs infected with *T. cruzi* or on rats infected with *T. lewisi* for two or three days and were then fed on clean animals. The lice passed part of each day on the experimental animal and were kept at night in tubes containing hairs of guineapigs or rats and fragments of blotting paper. It was found to be important to keep the temperature about 25°C. and the atmospheric humidity about 60°C. Even with these precautions the experiments could not be prolonged beyond 20 days.

Of 24 Melophagus fed on rats infected with *T. lewisi* 7 showed developmental forms in their mid-gut and 1 exhibited a permanent infection of the posterior gut. Of the 42 Melophagus fed on *T. cruzi* infected animals 8 showed cultural forms in the mid-intestine. Guineapigs and rats inoculated from the infected Melophagus became infected. *W. Y.*

i. Mazza (Salvador). Investigaciones sobre la enfermedad de Chagas. I. Hallazgo de tripanosomas en murciélagos del Chaco y Ledesma, Jujuy. Presenta identidad de estos flagelados con *Schizotrypanum cruzi*, Chagas, 1909. [**Studies in American Trypanosomiasis (Chagas's Disease). I. Discovery of Trypanosomes in Bats in Chaco and Ledesma, Jujuy.**]—*Universidad Buenos Aires: Misión de Estudios de Patología Regional Argentina Jujuy.* 1935. Publicación No. 22. pp. 1–11. With 6 figs. (1 coloured). [11 refs.]

ii. —— & Miyara (J. S.). II. Sobre el hallazgo de un nuevo edentado, huesped natural de *Schizotrypanum cruzi* en la provincia de Mendoza. [**II. Another Natural Host of** *T. cruzi* **in the Province of Mendoza.**]—*Ibid.* pp. 11–16. With 3 figs. [12 refs.]

iii. Romaña (Cecilio). III. Acerca de un síntoma inicial de valor para el diagnóstico de forma aguda de la enfermedad de Chagas. La conjuntivitis esquizotripanósica unilateral (Hipótesis sobre puerta de entrada conjuntival de la enfermedad). [**III. An Important Early Symptom of Chagas's Disease.**]—*Ibid.* pp. 16–28. With 5 figs.

iv. Mazza (Salvador), Miyara (S.), Basso (G.) & Basso (R.). IV. Comprobación de *Triatoma platensis* Neiva 1913 en la provincia de Mendoza. [**IV.** *Triatoma platensis* **Neiva in Mendoza Province.**]—*Ibid.* pp. 29–30.

A series of papers adding to our knowledge of Chagas' disease, its natural hosts and its vectors.

i. The author records the finding, for the first time in the areas concerned, Resistencia, Chaco, and Ledesma, Jujuy, of certain trypanosomes in bats of the species *Nyctinomus macrotis*. In both the places mentioned the local Triatoma have been found heavily infected with evolution forms of *T. cruzi*. " Some time ago " a human case of Chagas' disease was observed in Ledesma and according to the author, though the record has not yet been published, two of his pupils have just confirmed the existence of cases in Resistencia. He is of opinion that the forms found in the bats are also *T. cruzi*.

ii. That the armadillos, *Dasypus unicinctus*, *D. sexcinctus*, *D. novemcinctus* and *Chaetophractus vellorosus* are natural Brazilian hosts of *T. cruzi* has been known for some time. The parasite has now been found also in another armadillo, *Zoëdyus pichy caurinus*, captured in San Carlos, Province of Mendoza. The trypanosome was seen in blood smears. Histological examination of the organs proved negative, but inoculation of the blood into white mice resulted in a month in the appearance of *T. cruzi* in the circulation, and a second inoculated with the citrated blood of this also showed infection after a similar interval.

iii. Nine cases of Chagas' disease in children between 1 and 10 years of age are recorded. In all but one a very early symptom was oedema of an eyelid with no pain but with conjunctivitis. The parents usually ascribed it to the bite of an insect, a bug (vinchuca), and there is an associated adenitis, pre-auricular, parotid or submaxillary. The swelling may be very marked, so that the eye cannot be opened. Further examination may reveal rise of temperature, increased pulse-rate, enlargement of liver and spleen. The oedema may spread widely.

Experimentally, conjunctival inoculation may result in setting up the disease and the author suggests that this is the usual portal of entry, seeing that this conjunctivitis and local oedema is so frequently an initial symptom. [Observation of a larger series of cases would serve to show whether this ocular lesion occurs more frequently than would be explained by the bug biting the closed eyelids or near them and the child inoculating the wound by rubbing.]

iv. Examination of bloodsucking Hemiptera in the Province of Mendoza has shown that, besides *Triatoma infestans*, another species *T. platensis* is found. It was first reported in 1913 in the Santa Rosa department of this Province. More recently it has been encountered in other departments also, Las Heras, Lavalle and Guaymallén, in the compounds where goats are kept and in human dwellings; in the latter *T. platensis* was present together with *T. infestans* infected with metacyclic forms of *T. cruzi*. [It is not clear in the article whether this infection applied to both species or to *T. infestans* only.]

H. H. S.

Malamos (B.). Ueber Vorkommen von *Schizotrypanum cruzi* bei Affen in Niederländisch-Indien. [**The Occurrence of *T. cruzi* in Monkeys from Dutch East Indies.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Apr. Vol. 39. No. 4. pp. 156–171. With 16 figs. [23 refs.]

This paper records the discovery of *T. cruzi* in a number of Cynomolgus from Java.

After pointing out that hitherto *T. cruzi* has not been found in man or animals outside the American continent, the author states that whilst examining for malaria parasites a group of 10 young *Macacus cynomolgus*, which had recently arrived in Hamburg from Java, trypanosomes were found in two of them. A third was also proved to be infected through subinoculation of its blood into other monkeys. The remaining monkeys were examined for latent infection by means of the xenodiagnostic test of Brumpt, and still another was found to be infected.

None of the infected animals exhibited any signs of disease. The findings in the peripheral blood varied; sometimes scanty trypanosomes could be found for a number of days, and at other times the blood was negative. A detailed account is given of the morphology of the parasite and of its pathogenicity for other monkeys and various laboratory animals. *Triatoma infestans* were readily infected and the faeces of the infected bugs produced subacute infections in mice. Study of the pathological anatomy of infected monkeys revealed the usual foci of leishmania forms in the heart and skeletal muscles, and in the lungs, liver, kidney, spleen, lymph glands and suprarenals. In fact all the findings indicate that the parasite in question is identical with *T. cruzi*.

W. Y.

Reichenow (Eduard). Beiträge zur Kenntnis der Chagaskrankheit. [**Contribution to Knowledge of Chagas' Disease.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Nov. & Dec. Vol. 38. Nos. 11 & 12. pp. 459–477; 499–518. With 6 figs. [38 refs.]

In 1932 the author went to Guatemala to investigate the conditions of the workers on the plantations of Ludwig Nottebohm, especially in respect of malaria and hookworm. He soon found that Chagas' disease provided a good field for investigation, and the present paper describes the result of his work in this direction.

The author first worked in the neighbourhood of Las Viñas, which lies about 40 km. south of the capital of Guatemala. He found that the primitive dwellings of the plantation labourers were heavily infested with *Triatoma dimidiata*. Over the greater part of Guatemala the primitive rural houses are built of mud, and when the mud dries

deep fissures are formed which are ideal hiding places for the bugs. As the insects cannot be got at in these shelters the older huts are infested to an astonishing degree. Details are given regarding the habits of the Triatoma and their geographical distribution in Guatemala. They seem to occur everywhere, except in certain places in the west of the country near the Mexican frontier.

Wherever Triatoma were captured a certain number were found to harbour flagellates in their intestine. Apparently 29 to 35 per cent. of the insects were infected with a flagellate which animal inoculations showed to be *T. cruzi*. It was established that the infection spread chiefly directly from insect to insect through coprophagy. In 39 per cent. of the bugs a gregarine was found which could only be spread in this manner. It is presumably upon the frequency, or the reverse, of passage through the vertebrate host that the differences in virulence exhibited by various strains of *T. cruzi* depends.

Turning to the question of natural infections of vertebrates, the author writes that the chief sources of blood in the huts, apart from men, are dogs. Accordingly, the blood of numerous dogs was examined and in Las Viñas of 94 dogs 3 were found to be infected with *T. cruzi*; all the infected animals were about 2 months old, and as the 94 dogs included 12 of this age it appears that 25 per cent. of young dogs are infected. Among the older dogs only microfilariae were found on five occasions. Two armadillos and 14 bats were negative, and the trypanosome found naturally in monkeys belongs to a different species. The dog apparently is therefore the chief vertebrate host of *T. cruzi*. A large number of observations were made on the pathogenicity of Guatemala strains of *T. cruzi* for various laboratory animals and the results were compared with those given by a Brazilian strain; guinea-pigs, rabbits, mice, rats and dogs were used in this work. It was found that only in mice was the Guatemala strain moderately pathogenic; the Brazilian strain was much more pathogenic both for mice and young dogs.

The author next proceeded to make an exhaustive search for cases of human infection among children and adolescents. In the plantation village of Las Viñas the blood of about 100 young children was examined on three occasions and 3 were found to be infected. The infected children exhibited practically no symptoms and they remained free from signs of disease during an observation period of at least 1½ years. Notwithstanding this considerable infection rate (3 per cent.) among the children no instance of chronic Chagas' disease was found among the inhabitants of Las Viñas.

The last portion of the work deals with the distribution and significance of Chagas' disease. Las Viñas constitutes the most northerly point in the known distribution of the disease. Although the disease has been known for 25 years the number of cases discovered has been small. In view of this the author has collected together all the recorded cases in which a definite diagnosis (parasitic) has been made and has recorded the place where they were discovered on a map of South and Central America. In this map he has also indicated the distribution of Triatoma. As the result of his analysis Reichenow believes that the infection in man, notwithstanding the small number of cases yet recorded, must be extremely common in South and Central America. The course of the acute infection differs according to differences in virulence of the trypanosome strain in the various countries; as a rule, it is favourable and only exceptionally, as in the Brazilian

state of Minas Geraes, is it threatening. It would seem as if the infection, after the acute stage is over, recovers spontaneously, and that there is no real evidence of a chronic stage of Chagas' disease.

W. Y.

Villegas (Conrado). Dos nuevas observaciones de *Trypanosoma cruzi* en la Provincia de Córdoba. [**Fresh Cases of *Trypanosoma cruzi* Infection in the Province of Cordoba.**]—*Folia Biol.* Buenos Aires. 1934. Sept.–Oct.–Nov.–Dec. Nos. 42–43–44–45. pp. 200–201.

Many observers have remarked on the absence of symptoms in the Argentine in spite of infection with *T. cruzi*. The same held good in the two cases here recorded ; the trypanosomes were found by chance.

The author was sent by the Director of the Institute of Hygiene, Cordoba, to determine the blood and splenic indexes in the Departments of Cruz del Eje and Minas which were believed to be endemic foci of malaria. He examined the blood of 200 persons by the thick drop method and among them found *T. cruzi* in two, a woman of 23 years and a girl of three. In the former only a single trypanosome was seen in the preparation, in the latter a score or so ; both lived in Pichanas, Department of Cruz del Eje. Both persons appeared to be in perfect health. Inoculation of 1 cc. of the child's blood into the peritoneal cavity of a young white rat resulted twelve days later in the presence of trypanosomes in small numbers in the peripheral blood.

H. H. S.

Romaña (Cecilio). Tripanosomiasis americana y bocio endémico. Estado actual de la cuestión. [**American Trypanosomiasis and Goitre.**]—*Semana Méd.* 1935. Mar. 21. Vol. 42. No. 12 (2149). pp. 897–902. [13 refs.]

This article summarizes the present state of the question as to whether there is any aetiological connexion between Chagas' disease and enlargement of the thyroid.

The author gives a quotation from Chagas' description of the disease which led him to conclude that the goitre was of trypanosomal origin. He next enumerates the arguments in favour of the theory, with brief comments on each : (1) That the condition of myxoedema is often found in the acute cases and in the later chronic stages trypanosomes are present and the thyroid is enlarged. (2) That thyroid enlargement is common in regions where the disease was first studied, the northern Minas Geraes, and where other forms of the disease exist. (3) That the infectious theory of goitre has been widely accepted by those who have specially studied the condition and that " the goitre found in regions where Chagas' disease prevails is caused by the latter " [this would savour of a *petitio principii*]. (4) That intrauterine infection by trypanosomes would account for the congenital goitre observed in children inhabiting districts where Chagas' disease prevailed.

Of arguments against, the author gives the following : (1) That the myxoedema spoken of is found in human beings and even in animals who show no trypanosome infection. (2) That there are regions in Brazil and in the Argentine where the two diseases coexist, or are superposed and others where goitre has been known for a long time but where Chagas' disease is not met with. (3) The opposite

of the last, viz., that there are areas where the trypanosomiasis, both in acute and chronic stages, is present, but goitre is not observed. (4) That the pathology of the goitres associated with the trypanosome infection has not been closely studied in these districts till recently except in cases of chronic Chagas' disease, but now nothing characteristic has been found different from what is seen in endemic goitre in other parts of the world. (5) That in spite of all the experimental research carried out on this form of trypanosomiasis no investigator has recorded any predilection on the part of the parasite for affecting the thyroid gland, nor have they noticed hypertrophy of the gland as a result of their experiments. [The author does not include Kraus's paper among his references. Kraus, after some years' investigation, was very doubtful of any aetiological connexion between Chagas' disease and goitre (see this *Bulletin*, 1926, v. 23, p. 912).]

H. H. S.

Fitte (Oscar E.). Primer caso de tripanosomosis humana en la Prov. de La Rioja. [**First Case of Human Trypanosomiasis in La Rioja.**]—*Prensa Méd. Argentina.* 1935. Feb. 27. Vol. 22. No. 9. pp. 432–433.

The author has for some time been on the look out for cases of infection with *T. cruzi*, and when examining blood for malaria by the thick drop method has searched also for trypanosomes. He found them, though they were scarce, in the blood of a boy of 13 years showing no symptoms except some glandular enlargement. Their presence was confirmed by inoculation of 10 white mice each with 0·5 cc. of the patient's blood ; one died four days later, the other nine gave positive results. The case is put on record as it is said to be the first reported from the Province of La Rioja in the Argentine. *H. H. S.*

Chagas (Evandro). Infection expérimentale par le *Schizotrypanum cruzi* chez l'homme. [**Experimental Infection by** *S. cruzi* **in Man.**]—*C. R. Soc. Biol.* 1935. Vol. 118. No. 7. p. 718.

An experiment performed on a human being with the object of ascertaining whether *T. cruzi* is transmitted through the bites of infected reduviid bugs was negative.

Three larvae and one adult *Triatoma megista*, the faeces of which contained numerous crithidia and metacyclic forms of *T. cruzi*, were allowed to feed on the forearm of the patient, care being taken that no faeces were deposited on the skin during the meal. The patient, who was carefully observed for a period of 30 days, failed to show any signs of infection. As previous observations had shown that the incubation period of this infection in man is only 10 to 12 days, Chagas concludes from the present experiment that *T. cruzi* is not transmitted to man by the bite of Triatoma. *W. Y.*

Bonacci (Humberto). Nuevo medio de cultivo para el *Trypanosoma cruzi* Chagas, 1909. [**A New Medium for cultivating** *T. cruzi*.]—*Rev. Inst. Bacteriológ.* Buenos Aires. 1934. Mar. Vol. 6. No. 2. pp. 242–247.

The author gives three formulae, of nutrient agar differing very slightly. He calls them Nos. 1, 4 and 9. No. 1 is a nutrient broth with Witte's peptone 1·5, NaCl 0·5 and agar 1 per cent. No. 4 has

2·5 per cent. peptone and 0·7 per cent. NaCl, and No. 9 3 of peptone and 0·7 NaCl. The mixture is made neutral to litmus, heated to 115°C. for 20 minutes, filtered through cotton wool and placed in Erlenmeyer flasks, 100 cc. in each and sterilized in the autoclave at 110°C. for 20 minutes. This nutrient agar forms the basis of his medium to prepare which the agar is melted, cooled to 50°C. and to it are added 0·5 per cent. glucose and 5 per cent. sterile whole blood of a young guineapig and the medium distributed in test-tubes. The optimum temperature for cultivation is 25°C.

The author has successfully inoculated animals with such a culture and symptoms appeared after 10 days' incubation and the trypanosomes persisted in the peripheral blood for 39 days. The most sensitive animals for the experiments were puppies and next in order white rats, kittens and guineapigs. Noguchi's medium, he states, is not so good for isolation of the trypanosome, but is excellent for preserving the strains and has the further advantage of being able to adapt itself to temperatures above 25°C. The author claims that his medium is very useful for early diagnosis of suspected cases. *H. H. S.*

Dias (Emmanuel). [In Portuguese & French.] *Trypanosoma cruzi* ou *Schizotrypanum cruzi* ? [**Is *T. cruzi* or *S. cruzi* Correct Nomenclature ?**]—*Mem. Inst. Oswaldo Cruz.* 1934. Vol. 29. No. 1. In Portuguese pp. 203–215. With 1 fig. [42 refs.] In French pp. 217–227. With 1 fig.

This paper is devoted to a discussion of the systematic position of the parasite of Chagas' disease, known under the names *Trypanosoma cruzi* and *Schizotrypanum cruzi*, each of which has the support of authoritative writers whose opinions are critically examined by Dias.

The author himself maintains that the characters distinguishing this form from other trypanosomes provide sufficient grounds for recognizing it as a separate genus, under the name *Schizotrypanum cruzi*. These are (1) its intracellular situation in the tissues of the vertebrate host during multiplication, and (2) reproduction only in the leishmanial stage. The author, moreover, holds that *Schizotrypanum* is related to *Leishmania*, occupying an intermediate position between this genus and *Trypanosoma*. The latter genus is reserved for flagellates which multiply in the blood in the trypanosome stage. [It should be noted, however, that strictly speaking, the site in which a parasite develops is of no taxonomic value, the classification of animals being based on their morphological characters exclusively. The morphology of *T. cruzi* conforms to that of all trypanosomes, from which it differs only in its multiplicative phase. Since the stage in which reproduction occurs varies considerably in other trypanosomes, it cannot serve to separate *T. cruzi* from them generically. If this were done a number of other equivalent genera would have to be created. In view of these facts, it is advisable to retain Chagas' original name, *Trypanosoma cruzi*.] *C. A. Hoare.*

Zumpt (F.). Zur Systematik der *Glossina palpalis*-Gruppe. [**The Systematics of the *Glossina palpalis* Group.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Apr. Vol. 39. No. 4. pp. 141–156. With 10 figs.

Transgressing the limits of his subject as indicated in the title, the author first considers subdivisions of the genus *Glossina*, and, relying

on characters afforded by the genital armature in both sexes, raises the *fusca*, *palpalis* and *morsitans* Groups of NEWSTEAD to subgeneric rank, employing respectively for the three subgenera so constituted the names *Austenina* (sunk more than a decade ago by NEWSTEAD), *Nemorhina*, and *Glossina* (*sensû stricto*). A table is then given for the distinction of the species included under the subgenus *Nemorhina* (*i.e.*, the *G. palpalis* Group), among which are *G. fuscipes*—generally regarded, even by its author, as a subspecies of *G. palpalis*, but restored by Zumpt to specific rank—and what is described as *G. martinii*, sp. nov. The latter, the typical material of which was taken in Tanganyika Territory (at Bismarckburg, near the extreme southern end of L. Tanganyika), though indistinguishable from *G. palpalis* and *G. fuscipes* by means of external characters, exhibits certain differences, considered by the author to be of specific value, in the shape of the inferior claspers.

[Whether, in the absence of all other characters, slight differences in the inferior claspers are really of specific value is a matter which must be left to the individual opinions of experienced systematists. The present reviewer, at any rate, is inclined to think that, pending the crucial test of *mating*, it will be well to continue to regard *G. fuscipes* as a form of *G. palpalis*, and to treat *G. martinii* likewise.

The use by the author of the terms outer and inner *parameres* (borrowed from mosquito terminology, in which they are applied to parts of the penis) for the superior and inferior claspers is to be deprecated.] *E. E. Austen.*

NASH (T. A. M.). **The Identification of the Three Commonest Species of Nigerian Tsetse Fly.**—3 pp. With 5 diagrams. 1934. Aug. Printed by Survey Department, Lagos.

This is a useful two-page leaflet describing and illustrating by line blocks certain differences between *Glossina palpalis*, *tachinoides* and *morsitans*. It is intended for the use of those who have no knowledge of entomology. Clearly such leaflets as these might be of considerable value in many parts of Tropical Africa. *P. A. Buxton.*

NASH (T. A. M.). **The Effect of High Maximum Temperatures upon the Longevity of** *Glossina submorsitans*, **Newst., and** *G. tachinoides*, **Westw.**—*Bull. Entom. Res.* 1935. Mar. Vol. 26. Pt. 1. pp. 103–113. With 2 figs.

In the north of Nigeria the climate is extremely hot and dry in March and April. What is the effect of this on adult Glossina, exposed in cages to conditions prevailing in the shade ?

At the beginning of each month groups of freshly emerged fly (*G. submorsitans* and *tachinoides*) were put in small cages, and exposed to shade temperature in a hut with a good thatch roof but no sides : the conditions are approximately those which prevail in a dense thicket. The flies were offered an opportunity of feeding daily. Experiments were carried out in the four months January to April, the temperature rising steadily throughout this period. The mean length of life fell from about 25 days in January to about 3 in April. Moreover, a consideration of the number of deaths and of the maximum temperature on individual days shows clearly that temperatures above 100°F. (37·8°C.), and particularly above 103°F. (39·4°C.) are followed by a high mortality. It seems that *G. tachinoides* are killed by rather lower temperatures and shorter exposures than are *submorsitans*.

It is encouraging to observe that these figures, obtained under semi-natural conditions, agree in essentials with those which BUXTON and LEWIS obtained under strictly defined laboratory conditions [*ante*, p. 369]. It seems highly probable that the high temperature in the region where these experiments were carried out, causes a high mortality in nature at this season of the year. If this is so, then as the author suggests, a very restricted thinning of trees in the permanent breeding places might result in local extermination of the fly.

P. A. B.

MERKEN (G.). Pièges Harris. [**Harris Traps.**]—*Bull. Méd. du Katanga.* 1934. Vol. 11. No. 5. pp. 154–157.

It appears that the Belgian as well as the Congolese daily papers have been booming the Harris traps as capable of clearing the Belgian Congo of sleeping sickness. The author points out that ideal conditions for the traps are rarely to be found in the haunts of *G. palpalis*. These haunts are in deep, heavily shaded forest galleries, sunless for most of the day and it is not practicable to make clearings for the traps. In any case the traps will not catch all the tsetses. *A. G. B.*

JACONO (Igino). Osservazioni sui tripanosomi e proposta di una nuova classifica. [**A New Classification of Trypanosomes.**]—*Ann. di Med. Nav. e Colon.* 1935. Jan.–Feb. 41st Year. Vol. 1. No. 1–2. pp. 1–18. With 20 figs.

Having studied the somewhat striking trypanosomes which occur in frogs the author attempts a new classification of the group into two genera, the one (*Trypanosoma*) to include those of the type he has studied and the other (*Castellanella*) all other trypanosomes. There would seem to be little justification for this procedure which appears to the reviewer to be quite artificial. *C. M. Wenyon.*

GRALL (G.). L'action thérapeutique du service de la trypanosomiase en A.O.F. jugée par les Bandas de l'Oubangui-Chari : le " ballet de la maladie du sommeil."—*Ann. de Méd. et de Pharm. Colon.* 1935. Jan.–Feb.–Mar. Vol. 33. No. 1. pp. 144–146.

SCHILLING (Claus). Die Bekämpfung der Tsetsefliege im früheren Deutsch-Ostafrika.—*Deut. Med. Woch.* 1935. Mar. 15. Vol. 61. No. 11. pp. 427–428.

MALARIA.

WATSON (Malcolm). **Some Pages from the History of the Prevention of Malaria.**—*Glasgow Med. Jl.* 1935. Feb., Mar. & Apr. Vol. 5. Nos. 2, 3 & 4. pp. 49–70 ; 130–153 ; 202–220. [79 refs.]

Sir Malcolm Watson commenced his lecture with a sketch of the work in Malaya, begun in 1901, and described by Ross as the first successful anti-malarial work in the British Empire. He drew particular attention to the decrease in deaths from other diseases which followed the successful control of malaria. He stated that an important factor which contributed to his success was the combination of clinical observations made in the hospital with epidemiological observations made in the field ; he was himself physician, health officer and entomologist, there was perfect co-operation with the engineer. " I want to emphasize," he said, " that our success has come from the knowledge acquired not in the hospital alone, nor in the laboratory alone, but by co-ordinated work in all three, and it led to discoveries in clinical medicine, protozoology, ecology and epidemiology of fundamental importance in the prevention of disease."

While he was a busy practitioner and the sole European medical officer in a coast district a hundred miles long, Watson yet managed to make discoveries of inestimable value. " In my little laboratory I was breeding mosquitoes, discovering new species of mosquitoes, recognizing structures that enabled me to construct a key for the identification of the larvae of certain species of anopheles, a matter of great practical importance. In the field I was studying the biology of the insects. . . . As medical officer, I saw and treated the sick in hospital."

As a striking example of what can be accomplished by mosquito control, he retold in his lectures the story of Carey Island where control has been in force from the opening of the rubber estate in 1906. Carey Island is really a fresh-water swamp on clay soil, surrounded by salt water ; conditions which are notorious for producing the most appalling malaria. It has always remained healthy, and Sir Malcolm quotes his successor Dr. Barclay BARROWMAN who wrote in 1934, " On Carey Island, with a population of over 5,000 . . . there has been one child with enlarged spleen during the past five years, and she had arrived on the estate with the spleen already enlarged. The infection rate among the total population for the past five years has been under one-tenth per cent. per annum. . . . there is rapidly growing up a locally-born labour force—18 per cent. of the present population was born on the estate. There are over 1,500 healthy happy children, among whom the sick day rate last year was no more than 0·4 per cent."

After Watson had dealt successfully with the malaria of the coast and flat land, due to *A. ludlowi* and *A. umbrosus*, he was faced with the problem of malaria of the inland hills and ravines, carried by the stream-breeder, *A. maculatus*. " What the country required was some new method of preventing the disease. To this I now turned my attention . . . I had a deep conviction that this deadly *A. maculatus* could be exterminated if appropriate measures were adopted. So I devised a system of subsoil drainage of valleys. . . . The system proved a success . . . We still required a quicker and less expensive method of controlling malaria than subsoil drainage. This was provided by my discovery in 1914 of a mixture of mineral oils which

completely destroyed *A. maculatus* when applied once a week to fast-running streams. . . . The value of this discovery was quickly appreciated, and the use of this anti-malarial mixture spread throughout the peninsula, with the happiest result . . . most unfortunately, I did not publish this discovery until 1921. Had I done so, the story of malaria in many parts of Macedonia during the Great War might have been very different." After relating the success attained by his method, in the rubber estates of which he was in medical charge, the lecturer spoke of the work begun in Singapore in 1911. "This city was next off the mark. . . . Within the municipality in 1932 there were 41·25 miles of concrete channels, 72·63 miles of subsoil pipes, and over 300 miles of earth ditches; 18,682 gallons of anti-malarial mixture were used. . . . In the Federated Malay States the Government next took up the work, and in November 1911, the Malaria Advisory Board began work. . . . For the year 1926 . . . the expenditure on malaria by the F.M.S. Government was £104,400."

In speaking of prevention by treatment, the lecturer said, "There is, in my opinion, no antagonism and no competition between the various methods of preventing malaria. . . . In all campaigns anti-malarial drugs have a place." He spoke of the work of GORGAS in Havana and in Panama in terms of highest praise. "It had been proved that both malaria and yellow fever were carried by mosquitoes; and it had already been proved in Havana (1901) Klang (1901) and Ismailia (1902) that these diseases could be brought under control, or for all practical purposes abolished, when the mosquitoes carrying them were reduced below a certain number." *W. Fletcher.*

DE LANGEN (C. D.) & STORM (C. J.). **Observations on the Modern Medical Treatment of Malaria. A Clinical and Experimental Study.**—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 233–260. With 16 figs. on 12 plates.

HOOPS (A. L.). **Observations on the Prophylaxis and Cure of Malaria with Atebrin on Malacca Rubber Estates during Two Years (July 1932 to June 1934); with a Note on the Prevalence of Malaria on these Estates since 1925.**—*Ibid.* pp. 261–280. [32 refs.]

YAO (Y. T.) & JUNG SUN (C.). **Field Experiment on Malaria Treatment. A Comparative Study of the Therapeutic Value of the Various Anti-Malaria Remedies.**—*Ibid.* pp. 281–297. With 2 charts. [15 refs.]

WALCH (E. W.) & SOESILO (R.). **Malaria Control in the Netherlands Indies.**—*Ibid.* pp. 191–200. With 15 figs. (13, 1 coloured, on 7 plates).

SCHARFF (J. W.). **Anti-Mosquito Measures in the Northern Settlement of Malaya.**—*Ibid.* pp. 201–212. With 5 plates & 3 figs.

YAO (Y. T.) & WU (C. C.). **Antilarval Measures by the Use of Paris Green in a Selected Area of Nanking.**—*Ibid.* pp. 213–221. With 3 charts.

RUSSELL (Paul F.). **The Automatic Distribution of Paris Green for Control of Anopheles Larvae.**—*Ibid.* pp. 223–232. With 2 text figs. & 3 figs. on 2 plates.

YAO (Y. T.) & WU (C. C.). **One Year's Observation of *A. hyrcanus* var. *sinensis* in Nanking, 1933.**—*Ibid.* pp. 3–26. With 3 maps. 2 graphs & 2 figs. [12 refs.]

—— & LING (L. C.). **Epidemiological Study of Malaria in Nanking.**—*Ibid.* pp. 89–106. With 3 charts. [18 refs.]

JACKSON (R. B.). **The Anophelines of the Colony of Hong Kong. Some Observations on their Species, their Habits, and on the Results obtained from Dissections of Catches made on the Island and Mainland.**—*Ibid.* pp. 27–36.

Toumanoff (C.). Etude de l'indice maxillaire de Roubaud en tant que méthode pratique d'investigation sur les aptitudes trophiques des espèces anophélinennes d'extrême-Orient. [**Roubaud's Maxillary Index as a Practical Method of Investigation of the Trophic Aptitudes of Anopheles.**]—*Ibid.* pp. 37–51. With 9 figs. & 3 charts.

Walch (E. W.) & Walch-Sorgdrager (G. B.). **The Eggs of Some Netherlands-Indian Anophelines.**—*Ibid.* pp. 65–81.

Morin (Henry G. S.), Bader (H.), Monnier (E.) & Moreau (P.). Récherches sur la concentration en chlore du sang chez les paludéens au Tonkin. [**The Blood Chlorine in Malarials at Tonking.**]—*Ibid.* pp. 165–190. With 7 graphs. [49 refs.]

Williamson (K. B.). **Need for Action in Relation to the Biochemical Investigation of Anopheline Breeding Places.**—*Ibid.* pp. 83–87.

Many valuable papers were contributed to the section on malaria at the Nanking Meeting of the Far Eastern Association of Tropical Medicine. Of special note was a defence of quinine against the newer remedies by Professor de Langen : an account of malaria control in the Dutch Indies by the late Professor Walch ; malaria control in Penang by Dr. Scharff ; *A. maculatus* in Hong Kong by Dr. Jackson ; the maxillary index in the anopheles of Indo-China by Dr. Toumanoff.

Professor C. D. de Langen and Dr. C. J. Storm presented an account of a clinical and experimental study of the action of quinine, plasmoquine and atebrin upon the organs of the body. They argue that these drugs do not act directly on the parasites but probably indirectly by stimulating the natural defence reactions of the organism, and that therefore the question of the general action of these remedies on the organism is of great importance. As the indirect route of action is the most probable one, figures intended to prove the superiority of one remedy over another in the matter of destroying the parasites are completely worthless. " The results in London, Hamburg, Amsterdam and other places in Europe with individual treatment must in no way be regarded as giving guidance for treatment in the real malaria countries."

The three remedies differ in their action on the liver. (*a*) Quinine does not damage it, and even in undernourished persons it will not produce urobilinuria. (*b*) Atebrin produces no urobilinuria in healthy people, but urobilin appears if there is malnutrition and the liver is poor in glycogen. (*c*) In fatalities due to plasmoquine the liver is always damaged. " Quinine exerts a favourable action on the functions of many organs. . . This is of great importance for the treatment of malaria patients. In criticising other products offered as remedies for this disease, it is therefore not sufficient that we should ask ourselves if they are toxic for the various organs, but also if they possess the same good general properties possessed by quinine. Such properties are not yet known in the case of plasmoquine and atebrin."

The authors have carried out a series of experiments with *Macaca irus* (*Cynomolgus*) in investigating cardiovascular disturbances following injections of the three drugs. Several reports have already been published on the circulatory disturbances which may follow the therapeutic administration of atebrin. When atebrin or plasmoquine was perfused through the isolated heart of a monkey, the rhythm of the organ became irregular, then it stopped and perfusion with pure Tyrode's solution did not start it again. Quinine did not produce irregularity of the contractions, and when the heart was stopped by very strong solutions of the drug it could be started again by perfusion

with pure Tyrode's solution. The total quantity of fluid flowing through the coronary vessels per minute diminished after the addition of either plasmoquine or atebrin, but after the addition of quinine it increased. The vasoconstriction which follows plasmoquine and atebrin throws a strain upon the heart. " While the fall in blood pressure following quinine must certainly be attributed to a vascular dilatation, that caused by plasmoquine and atebrin appears principally due to damage of the heart's action." When the vasomotor centre is intact, stimulation of a sensory nerve is followed by a rise of blood pressure. This reflex is not abolished by quinine. " That the reflex disappears after plasmoquine and atebrin must be attributed to a direct toxic action of these drugs on the vasomotor centre. . . both atebrin and plasmoquine, but especially the latter, are more toxic for the heart and vascular system than is in general admitted. . . . Moreover, since the administration of these drugs by routes other than the mouth is becoming more and more fashionable, it may be expected that untoward side-effects on the part of the circulation and respiration will become more and more common. . . . Apart from the direct, injurious organotropic action [of plasmoquine and atebrin] on the organs themselves, for instance the liver, it is also possible that in this way indirectly the development of that natural immunity on which recovery depends could be retarded." While quinine employed clinically restores extrasystolic arhythmias to normal rhythm, atebrin and plasmoquine produce such irregularities themselves. It is therefore advisable that when atebrin and plasmoquine are administered, quinine should be given with them because of its steadying effect upon the circulation.

This paper was followed by one in which Dr. A. L. Hoops gave an account of the great success of atebrin as used on the rubber estates of Malacca (see this *Bulletin*, Vol. 31, p. 695). He concludes that: " Atebrin is the best drug available for the treatment of all types of malaria in Malaya, especially in the case of controlled populations. . . . Atebrin is greatly superior to quinine in the prevention of relapses ; judging by present experience with atebrin, relapse rates do not exceed 5 to 8 per cent. in subtertian, and 5 to 16 per cent. in benign tertian malaria. . . . On estates, the cheapest and best measures are to continue antimalarial work in the danger zones, and to treat cases of malaria with atebrin. . . . A short course of plasmoquine, not exceeding 0·03 gram daily for from 5 to 8 days, should be given after atebrin treatment in subtertian malaria." [See p. 418 above, and also Hecht and Eichholtz in this number.]

Dr. G. T. Yao and Dr. C. Jung Sun reported on the treatment of 281 cases of malaria with different drugs. The drugs employed were totaquina types I and II, atebrin, quinoplasmoquine, and quinine. All of them were found equally effective in reducing the number of parasites, with the exception of crescents, in all three types of infections. Vomiting was the only toxic symptom ; this occurred in 5·5 per cent. of the atebrin treated cases and in a smaller proportion of those treated with the other drugs. Quinoplasmoquine was the most effective in reducing the size of the spleen.

Professor E. W. Walch and Dr. R. Soesilo told the story of the successful struggle against malaria in the Netherlands Indies. Success has been won by antilarval control, and they write, " The value of *antilarval measures* for the control of malaria has been very much discussed in recent years and we therefore wish to emphasize that the improvements mentioned above have been obtained through antilarval

measures." Malaria prevails in its worst form in the coastal zone. (1) The mangrove swamps are often free from malaria until they are interfered with, but, as soon as they are cleared, and the flow of water is hampered by footpaths, roads, and railway embankments, *A. ludlowi* var. *sundaica*, the most dreaded vector, and *A. subpictus* breed in the sunny, stagnant, brackish waterpools. (2) In other places, tides and currents lead to the silting up of the mouths of rivers ; behind the sand bars, lagoons are formed, where floating algae develop in the brackish water and provide ideal breeding places for *A. ludlowi*. Sometimes this silting has been prevented by building piers to divert the sand, but the best way to deal with a river which does not carry enough water to keep its mouth open is to connect it with a more powerful stream by digging a canal parallel to the coast line. This method is not always possible, and filling, canalization, etc., have been employed. (3) The marine fishponds used to be responsible for very severe malaria. An edible fish called " Bandeng " is raised in these ponds, and formerly *A. ludlowi* bred freely among the floating algae on which the bandeng fed ; the weeds protected the larvae from the small larva-destroying fish, *Panchax panchax*. These ponds have been dealt with by periodically draining them into the sea at intervals of about a month. This kills the floating algae and promotes the development of bottom algae which provide equally good nourishment for the bandeng. When the bottom algae float to the surface as the ponds refill, they form patches of compact scum. No larvae can breed in these patches, and the larvae in the open water between them are destroyed by their enemies the *Panchax*. (See *Bulletin*, Vol. 27, p. 640.) (4) The inland, fresh water fishponds, where " gorami " and " gold-fish " are raised for food are also responsible for much malaria which is carried in some places by fresh water *A. ludlowi*, and in others by *A. hyrcanus* var. *nigerrimus*. These inland ponds cannot be dealt with like those on the coast by opening sluice gates and letting them empty themselves into the sea. In some places, ponds situated on terraced hill sides have been drained, but elsewhere the economic loss entailed by destruction of the fishing industry could not be faced. Here again the mosquito larvae are sheltered by the aquatic vegetation ; this is not used as a food by the fish—these feed on leaves and vegetables thrown into the ponds for the purpose. The fish-expert, REYNTJES, has discovered a fish, the so-called " Tawes " (*Puntius javanicus*) which feeds voraciously on the submerged vegetation, and soon causes it to disappear. Pictures are given showing first, a pond covered with weeds before the introduction of tawes, and secondly, the same pond later on after it had been cleared of vegetation by their agency. (5) Ricefields present another problem ; generally speaking the wet ricefields are not dangerous, provided that they are supplied not only with efficient irrigation, but also with good drainage. The water on the coastal ricefields becomes brackish when irrigation is insufficient, and *A. ludlowi* breeds in them. Some of the valleys inland, lying at an altitude of about 1,000 feet, are watered by irrigation. At first, they were very fertile, and the natives exhausted the soil by too frequent planting ; later, they became waterlogged and poor, because adequate provision for drainage had not been made. *A. aconitus* bred in the flooded fields ; large areas were abandoned and formed pestilential swamps ; the spleen rate was between 80 and 90 per cent. The measures adopted were attended with astounding success, they were : (*a*) A drainage system, (*b*) cleaning the grassy irrigation ditches

which bred *A. aconitus*, (*c*) the planting of rice only once a year, and that in the wet season, so that during the dry season the plain was dry and anopheles breeding impossible. As a result of this, the spleen rate of Tjirandjang which was 88 in 1918, was only 1 in 1931, while it was 98 in a neighbouring district where nothing had been done. (6) In the hilly and mountainous districts of the Netherlands Indies, the carriers are *A. maculatus* and *A. aconitus*, as in the Malay States, and the methods used there have been adopted.

Dr. J. W. Scharff, Senior Health Officer, Penang, described how 15½ square miles, embracing practically two-thirds of the population of *rural* Penang, had been " insured against the risk of malaria infection." The cost is heavy : a sum of $50,000 (£5,833) was first made available for anti-mosquito work in 1924 ; this annual provision was repeated in 1925 and raised to $75,000 (£8,750) in later years. The method adopted is to oil the breeding places of dangerous mosquitoes for a distance of half a mile from the outskirts of the village or area which is being dealt with ; the proximal ravines are then drained and the oiling areas are extended further into the country, and are gradually linked up with other protected areas. A great deal of needless oiling is saved by reducing the area of the swamps and seepages in ravines. This is done by means of open drains dug along the edge, or contour, of the slope from which the water rises. Permanent anti-malaria drainage has been carried out in some populous areas ; but, except under special circumstances, no scheme is undertaken unless permanent drainage can be completed for the price of 5 years oiling, or unless the whole of the anti-malaria work within the area can be carried out for under a dollar per head of the population served. Paris green has been found definitely less efficient and more costly than oil in the control of *A. maculatus*, the principal Malayan carrier. Earthen wells in which mosquitoes breed are treated with petrol once a week. Two ounces stirred in with a stick are sufficient for a well 4 feet in diameter, and after half an hour, no taste or smell remains. The wells used for irrigating gardens on the slopes of Penang Hill were formerly the source of much malaria. It has been found that when these are freed from aquatic vegetation, and filled by means of water splashing into them from a height of a few feet, no dangerous larvae can breed there. The effect of the measures adopted " has been to transform the appearance of villages. In place of miserable and weakly children there are now sturdy youngsters. Squalor that was induced by sickness has given way to comfort and good health."

Drs. Y. T. Yao and C. C. Wu employed a 1 per cent. mixture of Paris green in road-dust as a larvicide in a selected area of Nanking with a population of 782, between August and December 1933. The incidence of both the adults and larvae of *A. hyrcanus* (the only anopheles) was greatly reduced. Dr. P. F. Russell described an automatic distributor for Paris green, which is fixed over a stream and is worked by a paddle-wheel turned by the current. (See this *Bulletin*, Vol. 30, p. 864.) Drs. Y. T. Yao and C. C. Wu gave the results of their observations on *A. hyrcanus* var. *sinensis* which is the only anopheles in Nanking. Out of 11,071 dissected, gut infections were found in 6. A number of laboratory-bred specimens were fed experimentally, with the result that some of them became infected with *P. vivax*. None of those fed on subtertian and quartan cases became infected. The authors found that *A. sinensis* would breed almost anywhere, but preferred water with plenty of vegetation, plenty of sunshine, still and clear, with a pH between

7·2 and 7·4. In a survey conducted by Dr. YAO and Dr. L. C. LING the spleen rate among the children was found to be 2·46. *P. vivax* accounted for 67 per cent. of all infections.

Dr. R. B. JACKSON presented a report on the anopheles of Hong Kong. He has made some interesting observations on the behaviour of *A. maculatus* in the colony. This mosquito is met with in hill streams throughout the year and constitutes the majority of the catch in these places. It is the most important carrier in Malaya, but in Hong Kong it is relatively harmless for it rarely comes into houses to bite man. This is not to be explained by the presence of large quantities of cattle, because there are few present. It is curious that, in Hong Kong, *A. maculatus* has been found in streams polluted by cow-byres, and in streams flowing through manured land. *A. minimus*, one of the two principal malaria carriers of Hong Kong, breeds in irrigation ditches and streams of flat grade amongst or near the hills. *A. jeyporiensis*, the other important carrier, breeds in abandoned terraced rice fields among the hills throughout the year, and in other rice fields when they are laid fallow in the autumn. The range of flight of this mosquito much exceeds half a mile. *A. hyrcanus* breeds in stagnant water with vegetation. It is not an important carrier, but both this mosquito and *A. maculatus* can carry malaria under exceptional conditions such as are met with in large camps of labourers.

Dr. C. TOUMANOFF reported on the maxillary index of the anopheles of Indo-China. The results of his investigation support the theory of ROUBAUD, to the effect that this index is low in androphilous species. The author found that the index in the harmless, or relatively harmless, species differed distinctly from that of dangerous species, such as *A. minimus*. The maxillary index of *A. barbirostris*, *A. vagus* and *A. subpictus* was high, and it was found by means of precipitin tests, carried out in conjunction with Dr. J. MESNARD, that these mosquitoes fed on the blood of animals, while, on the contrary, 86·48 per cent. of the *A. minimus* examined were found to contain human blood. It was concluded that the maxillary index is a very valuable indication of the habits of an anopheline species.

Dr. E. W. WALCH and G. B. WALCH-SORGDRAGER contributed a paper on the eggs of some Netherlands-Indian anophelines. They observed marked differences between the eggs of *A. subpictus* in British India (where an infected specimen has never been found) and those of the Netherlands Indies (where it is sometimes a carrier).

Dr. Henry G. S. MORIN and his colleagues contributed a paper on the occurrence of corpuscular hyperchloraemia in malaria (this *Bulletin*, Vol. 31, p. 459) and Dr. L. A. ROBIN one on premunition among labourers working on estates (*loc. cit.*, Vol. 32, p. 142).

A paper was received from Professor J. B. WILLIAMSON urging that action should be taken with regard to the biochemical investigation of anopheline breeding places, and the Congress passed the following resolution :—

"The Ninth Congress of the Far Eastern Association of Tropical Medicine, recognizing the pressing need for co-operative investigations in the problems of malaria control wishes, in particular, to emphasize and direct attention to the fundamental importance in malarial epidemiology of studying bio-chemical changes occurring in the breeding places of anopheline mosquitoes.

"This Congress considers that advances of practical utility in the control of malaria might be made if the data obtained by workers in the countries of the Far East were made comparable.

" It is resolved, therefore, ' that, with the consent of the Governments concerned, such investigations, conducted in various countries, be co-ordinated through the appointment of a joint committee of chemists and malariologists resident in these countries.'

" It is recommended that this Committee should be invited to formulate the general lines upon which bio-chemical investigations shall proceed, and that they should be asked to report to the Director of the League of Nations Far Eastern Bureau concerning the principles and methods of study which are likely to be most profitable and from time to time concerning the results achieved from this application.

" The following experts shall be requested to serve as honorary members of this Committee.

" (1) Dr. R. Soesilo, Chief of Malaria Survey of Netherlands Indies and (Miss) Dr. C. Hyman, representing the Netherlands East Indies.

" (2) Dr. H. G. Morin, Directeur du Service du Paludisme en Indo-chine, Institut Pasteur de Saigon and Dr. Bader, Chemist of Malaria Service, representing French Indo-China.

" (3) Dr. A. Neave Kingsbury, Director, Institute for Medical Research, Kuala Lumpur and Dr. J. L. Rosedale, Professor of Biochemistry, College of Medicine, Singapore, representing British Malaya.

" Furthermore, this Committee shall be empowered to co-opt other workers experienced in this field of study so as to extend this investigation throughout the countries of the Far East." *W. F.*

British Medical Journal. 1935. Mar. 23. p. 590.—**The Malaria Epidemic in Ceylon. First-Hand Experiences.**

The epidemic was due to a drought, which converted rivers into a series of pools.

Dr. Wigglesworth has recently visited Ceylon, and in March he gave an address at the London School of Tropical Medicine and Hygiene on the subject of the epidemic in that island. He said that he felt that the Ceylon Medical Department had organized the distribution of quinine and the extension of the facilities for treatment with a rapidity and smoothness which had not received the commendation it deserved. The authorities sent sanitary inspectors round the districts and on the basis of their reports temporary centres had been established. The epidemic was mainly due to a drought which dried up the rivers until nothing remained but a series of pools in which *A. culicifacies* bred. The same drought which caused the malaria brought about failure of the rice crop with considerable destitution, and it was evident that relief would have to be undertaken on a more extensive scale. The town of Kurunegala, where antimalarial measures had been carried out for a number of years, was badly hit. Would it have been possible to prevent the epidemic ? To have prevented the breeding of *A. culicifacies* over 300 miles of river and an indefinite area of streams by canalizing and oiling the pools would have been a far vaster undertaking than anything so far attempted for the control of malaria.

W. F.

de Silva (Stanley). **Observations on Some Interesting Cases occurring during the Malaria Epidemic in Ceylon.**—*Jl. Trop. Med. & Hyg.* 1935. Mar. 15. Vol. 38. No. 6. pp. 66–72. With 9 charts.

The author gives an account of the epidemic as he saw it in the wards of the General Hospital in Colombo. " The predominant parasite in

the epidemic was the malignant tertian parasite, and nearly 95 per cent. of the cases were so infected. [This statement cannot be applied to the epidemic as a whole, outside the hospital.]. . . . The most characteristic feature of the epidemic was the frequency with which cerebral and nervous symptoms appeared. . . . Another striking feature was the slow pulse, particularly in the comatose cerebral and algid type of case, a pulse of 80 or 90 per minute with a temperature of 103° to 104°F was quite common." Gastro-intestinal symptoms were very frequent ; nausea, vomiting, and watery stools with blood and mucus were seen in a large number of patients. These symptoms disappeared with malarial treatment. Many patients showed " pneumonic symptoms." All the patients with malignant malaria and cerebral symptoms had low blood-pressure. Intravenous quinine lowers the blood pressure still further ; " this was responsible for the tragic results seen in the wards in cases treated with quinine intravenously, some patients dying soon after, and even during, the injection " ; some were saved by adrenalin. Details are given of 13 illustrative cases of acute malaria. *W. F.*

McDonald (W. M.). **The Malaria Epidemic in Ceylon.** [Correspondence.]—*Brit. Med. Jl.* 1935. May 11. pp. 1001–1002.

Dr. McDonald of Antigua, while admitting that it would have been impossible to have prevented the breeding of *A. culicifacies* in Ceylon by the usual methods of antilarval control, considers that it might be possible to prevent future epidemics by concentrating on the destruction of adult mosquitoes in the houses. *W. F.*

Copeland (A. J.). **The Muruts of North Borneo. Malaria and Racial Extinction.**—*Lancet.* 1935. May 25. pp. 1233–1239. With 11 figs. (2 maps).

The aboriginal Muruts are being exterminated by malaria.

The Muruts were formerly called " head-hunters " because they raided each other's villages to secure their enemies' heads. This is an affair of the past, and under wise guidance by European district officers they have become a docile, friendly people. They live in the dense jungle of the southern part of the interior of British North Borneo ; they support themselves by hunting and fishing, and they number about twenty-two thousand. " Their debilitated physique is everywhere associated with highly endemic latent malaria," and their numbers have been steadily decreasing during the past eight years. Their neighbours, the Dusuns, on the other hand, are increasing. The Dusuns live in a more open environment in the upland plains and jungle of the north ; they are husbandmen who keep cattle and grow rice. The author attributes the decline of the Muruts to malaria and he counsels that some £5,000 should be spent annually on quinine, instead of £57 as at present, and that the head tax of 2s. 4d. per annum should be abolished. The upsetting of the equilibrium between these primitive people and the jungle in which they live seems to have been due to the clearing of forest, and the introduction of virulent strains of malaria by labourers imported from Java. *W. F.*

Greenfield (Gregor). Beitrag zur Frage der Malaria in Persien. [**Malaria in Persia.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. June. Vol. 39. No. 6. pp. 257–260.

A study of malaria as met with in Persia.

Malaria is the commonest disease in Persia. The author was stationed in the town of Malayer (Dowletabad), where the incidence of malaria amongst the population was over 20 per cent. Malaria was frequently complicated with pneumonia, pulmonary tuberculosis and dysentery. The diagnosis is often difficult as the symptomatology of malaria is very indefinite. Of 493 cases investigated 75 per cent. were benign tertian, 20 per cent. quartan and 5 per cent. malignant tertian. Purpuric symptoms were comparatively common : profuse bleeding from nose, haemorrhages under skin and mucous membranes, into muscles, also from the stomach, bowels and kidneys ; the latter occurred in the severe cases. Scurvy could be excluded. More rarely cases of convulsion and coma occurred, and generally ended fatally. Quinine often failed even when given by injection. *E. D. W. Greig.*

Chaĭkin (V. I.) & Enikolopov (S. K.). **A Short Epidemiological Description of Daghestan.**—*Med. Parasit. & Parasitic Dis.* Moscow. 1935. Vol. 4. No. 1–2. pp. 142–147. [In Russian.] [Summarized in *Rev. Applied Entom.* Ser. B. 1935. June. Vol. 23. Pt. 6. p. 167.]

" In Daghestan, malaria is rife and epidemics are favoured by the presence of large accumulations of water in irrigated rice-fields, swamps formed by small rivers and mountain streams, reservoirs in orchards, and neglected wells, filter pools, etc. The topography of 7 districts is discussed, with special reference to the breeding places of mosquitos and the prevalence of the disease. Of the Anophelines found in Daghestan, *Anopheles maculipennis*, Mg., was the most common and widely distributed. The adult males occurred from about the middle of May until the end of October. The larvae were found in all types of breeding place, but were most numerous in rather shallow water with a pH of 6·8–8 and a carpet of vegetation at the bottom. When larvicidal measures were carried out within a radius of 3 miles from some inhabited spot, the mosquitos bred in tubs and other receptacles for rainwater. *A. sacharovi*, Favr, which bred in places with dense tall vegetation rising above the surface of water, predominated in places where there was much subsoil fresh or mineral water. *A. hyrcanus*, Pall., came next in order of abundance, but *A. algeriensis*, Theo., was prevalent in some localities and, unlike the other mosquitos, sometimes occurred in shaded accumulations of water densely covered with reeds and having a peat bottom. *A. claviger*, Mg. (*bifurcatus*, auct.), *A. superpictus*, Grassi, and *A. plumbeus*, Steph., were rare."

Lisova (A. I.) & Eskin (V. A.). Infektion von *Anopheles maculipennis* var. *sacharovi* F. durch Malariaplasmodien in natürlichen Bedingungen in einem Reisfeldbezirk Uzbekistans. [**The Infection with Malaria Parasites of *A. sacharovi*, Favr, under Natural Conditions in a Rice-cultivating Region in Uzbekistan.**]—*Mag. Paras. Inst. Zool. Acad. Sci. URSS.* Leningrad. 1932. Vol. 3. pp. 49–62. With 4 figs. & 1 graph. [In Russian. German summary.] [Summarized in *Rev. Applied Entom.* Ser. B. 1935. Feb. Vol. 23. Pt. 2. pp. 49–50.]

" This is an account of work carried out during a severe epidemic of malaria in July–November 1930 in a village of the Tashkent district.

Favourable breeding conditions for mosquitos are afforded by neglected rice-fields and by a defective irrigation system, vast expanses of water being formed, much of which is covered with dense vegetation. . . .

" Adults of *A. sacharovi* taken in dwellings were dissected after 4–6 days till the end of August, and after 8–10 days from September till November. Of 556 examined, 36 contained oöcysts or sporozoites, or both. The last infected mosquito was taken on the 18th September. The sporozoites usually occurred in the thorax and abdomen as well as in the salivary glands. The rate of infection was highest in August.

" In one instance no malaria parasites could be observed in the blood of patients suffering from primary malaria, whereas they were found in mosquitos taken in the same room. This suggests that the occurrence of the parasites in mosquitos might serve as supplementary data in diagnosis.

" Some of the mosquitos, particularly those taken in mosquito-nets in September, were infested with Nematodes, which were usually present in the Malpighian tubes and sometimes completely blocked them."

Langton (E. A. C.). **Some Observations on Infants and Young Persons in Bunyoro, Uganda.**—*East African Med. Jl.* 1935. Jan. Vol. 11. No. 10. pp. 316–325.

Quartan is the most common infection in infants. Benign tertian is very rare.

Sixty-five infants, none of whom showed any symptoms of malaria, were examined. Forty, 61·6 per cent., had enlarged spleens and 34, or 52·3 per cent., had parasites in their blood. Twenty-two were infected with *P. malariae* and 12 with *P. falciparum*. *P. malariae* was responsible for the largest spleens ; this parasite became less common as the children grew older and was rarely seen after the age of 12. Among children under 5 years, 20 had quartan gametocytes in their blood, while only 2 had crescents. *P. vivax* was only found once in about 220 positive cases. There was a marked drop in the spleen rate after the age of 15. *W. F.*

Wilson (D. Bagster) & Wilson (Margaret E.). **Infections with *Plasmodium ovale* Stephens, in Tanganyika Territory.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1935. Mar. 8. Vol. 28. No. 5. pp. 469–474.

These cases of infection with *P. ovale* were found in natives during a survey made in the northern part of Tanganyika. Twenty-seven persons, among several thousand examined, were found to be infected with this parasite. Only one of the 27 was ill ; this was a case of malarial coma due to a mixed infection with *P. ovale* and *P. falciparum*. Gametocytes are more frequently present and more numerous than in infections with other species. *W. F.*

Hanson (Henry), Boyd (Mark F.) & Griffitts (T. H. D.). **Some Factors in the Epidemiology of Malaria.**—*Amer. Jl. Public Health.* 1935. Feb. Vol. 25. No. 2. pp. 156–161. With 1 fig.

This concerns malaria in Florida.

The anopheles are : *A. quadrimaculatus*, A. *crucians*, two varieties (fresh and salt water), *A. punctipennis*, *A. atropos*, *A. walkeri*, *A. barberi* ; all of them are potential vectors, but *A. quadrimaculatus* is far the most important. The greatest concentration of cases occurs in the northern counties, where the land is underlaid by limestone, and

where ponds, lakes and " sinks " are numerous. The spleen index taken in these regions, in 1931, was 25·6 per cent. The incidence is almost entirely rural. During the past 2 years (1932–34) 15,257 school children have been examined by the thick film method and 6·1 per cent. were found to be infected ; 70 per cent. with subtertian, 21 per cent. with benign tertian, 0·2 per cent. with quartan. *W. F.*

BALFOUR (M. C.). **Malaria Studies in Greece. Measurements of Malaria, 1930–1933.**—*Amer. Jl. Trop. Med.* 1935. May. Vol. 15. No. 3. pp. 301–330. With 2 charts and 1 map.

A review of the published reports of malaria in Greece since 1905 indicates that epidemics of malaria recur at intervals. In 1930, there was a condition of low endemicity ; in 1931, there was a severe epidemic ; in 1932, there was a state of high endemicity ; in 1933, a low stage of endemicity was reached once more. Since 1921, 5·6 per cent. of the total deaths in Greece have been caused by malaria. Quinine importations have varied from 20 to 50 tons annually. At ordinary times *P. vivax* and *P. malariae* are the common species of parasite, but *P. falciparum* takes the lead in epidemics. No major area in Greece is free from the disease. The spleen index, determined by the author, was 35·6, and the parasitic index 17·4 ; this was in 1933, a quiescent year of low endemicity. The rates were much higher in the small villages than in the towns. The relative percentages of the three species were : *P. falciparum* 38, *P. vivax* 34·5, *P. malariae* 26·5. The principal malaria season extends from the end of July to October. The seasonal wave in Greece is, on the average, longer, and continues later in the year than is the case in Italy and other European countries. It is believed that the explanation lies in the greater prevalence of *A. superpictus* in Greece. This anopheles has its greatest density in the autumn. *W. F.*

TRAUSMILLER (O.). Le paludisme dans les Iles de l'Adriatique : Krk, Rab et Pag. [**Malaria in the Adriatic Islands.**]—*Bull. Office Internat. d'Hyg. Publique.* 1935. Feb. Vol. 27. No. 2. pp. 291–303. With 2 maps & 2 figs. on 1 plate.

An example of control by means of Gambusia [see also this *Bulletin*, Vol. 30, p. 865].

The islands along the coast of Yugoslavia are malarious, while the mainland is comparatively healthy. The Dalmatian islands, on the contrary, are healthy while the mainland is malarious. The chief carrier in the three islands is *A. maculipennis*. In the island of Krk, there are no rivers and the rain sinks quickly into the porous soil, except in certain districts characterized as " red soil " districts. This red soil is less porous, and in these districts there are numerous ponds, or " *lokvas* " which furnish the sole supply of water for agricultural purposes. They become very foul through contamination by cattle, but nevertheless *A. maculipennis* breeds in them prolifically. Gambusia were first put into these lokvas in 1924, and they multiplied rapidly. The ponds were soon cleared of larvae, and the incidence of malaria was so much diminished that the distribution of quinine, which was formerly the principal method of combating malaria, became largely superfluous. In dry seasons many of the lokvas dry up and the fish perish ; consequently owners have been made responsible for keeping their ponds clear of weeds and stocked with Gambusia.

The situation in the island of Rab which lies further south is quite different. Here there are numerous streams which come down from the hills and meander through marshy plains. Some drainage work has been carried out near the town, but treatment with drugs constitutes the principal method of dealing with malaria. Two years ago, treatment with atebrin and plasmoquine was introduced, and since then there has been a striking reduction in the amount of malaria.

In the island of Pag there are lokvas in the hills, and two brackish lakes in the marshy plains. Here again Gambusia has proved an efficient means of control, but if the Gambusia are destroyed, malaria returns ; for example, the inhabitants sometimes throw the stems of a euphorbia into the lakes in order to stupify the eels which then float to the top and are easily caught. Where this has been done, the Gambusia have been killed, anopheline larvae have thrived and malaria has increased. *W. F.*

GIOVANNOLA (Arnaldo). *Plasmodium ovale* **considered as a Modification of** *Plasmodium vivax* **after a Long Residence in the Human Host.**—*Amer. Jl. Trop. Med.* 1935. Mar. Vol. 15. No. 2. pp. 175–186. With 11 figs. [19 refs.]

The author does not accept *P. ovale* as a valid species.

This communication begins with a very useful critical survey of the cases of *P. ovale* infection which have been reported up to the present time, including the case reported by CRAIG in 1900. The author has compared the original Wagner-Jauregg strain of *P. vivax* with JAMES'S strain of *P. ovale*, and he writes, " In conclusion the study of the Wagner Jauregg strain of *P. vivax* which has been passed for 15 years directly with blood from one man to another shows a parasite practically indistinguishable from the usual description of *P. ovale*. . . . *P. vivax* as we observed it in chronic infections and in inter-human passages is practically indistinguishable from the usual descriptions of *P. ovale*. . . . We must consider these modifications as due to the long residence in the vertebrate host in which the parasite had adapted itself by modifying its biology. . . . At present we have not enough proof to accept *P. ovale* as a fourth human *Plasmodium*." *W. F.*

JAMES (S. P.), NICOL (W. D.) & SHUTE (P. G.). **The Specific Status of** *Plasmodium ovale* **Stephens.**—*Amer. Jl. Trop. Med.* 1935. Mar. Vol. 15. No. 2. pp. 187–188.

The authors give the reasons why *P. ovale* is to be regarded as a separate species :—

(*a*) Its morphology differs from that of the other 3 species and the differences persist when the parasite is passed from person to person by direct blood inoculation.

(*b*) The character and arrangement of the pigment in the oocysts found on the stomach wall of the mosquito, 72 hours after feeding, is specifically diagnostic. The sporozoites are much smaller than those of *P. vivax*.

(*c*) The morphological character of the parasite, the periodicity of its asexual cycle in man, and the characteristic clinical course of the disease which it causes, are not altered by repeated passages through insect and human hosts.

(*d*) *P. ovale* is immunologically distinct from the other species of malaria parasites. Patients who are immune to all the three ordinary types are not immune to *P. ovale*.

(*e*) The clinical course of a first attack of malaria when it is due to *P. ovale* is different from a first attack due to one of the other species.

W. F.

Stratman-Thomas (Warren K.). **Studies on Benign Tertian Malaria. 8. Observations on Splenomegaly.**—*Amer. Jl. Hyg.* 1935. Mar. Vol. 21. No. 2. pp. 361–363.

These observations were made on patients who were given a single primary therapeutic infection with *P. vivax*. The conclusions reached were that (*a*) the degree of splenic enlargement is proportional to the duration of the primary attack. (*b*) After the cessation of the clinical attack, the spleen quickly decreases in size. (*c*) " If the clinical attack subsides but the maximum degree of splenomegaly persists there is possibility of a relapse." (*d*) Since splenic enlargement is transitory spleen surveys should be made at the height of the malaria season.

W. F.

Boyd (Mark F.), Stratman-Thomas (W. K.) & Kitchen (S. F.). **Studies on Benign Tertian Malaria. 9. An Instance of Natural Refractoriness in a Caucasian to Inoculation with** *Plasmodium vivax*.—*Amer. Jl. Hyg.* 1935. Mar. Vol. 21. No. 2. pp. 364–365.

The patient, a white man who came from a place 95 miles from Tallahassee, was bitten on three occasions by numbers of mosquitoes of proved infectivity. The results were always negative. The strain used was the McCoy strain of *P. vivax*, which had its origin in a place within 12 miles of Tallahassee. The patient was then bitten by mosquitoes infected with the mild Steadman strain with the result that parasites were found in his blood 17 days later and persisted for 6 days in small numbers. There were no clinical symptoms and the temperature never approached 100°F. The patients had had three attacks of malaria during the previous six years. The authors conclude that this demonstrates the natural occurrence of homologous tolerance as well as some protection against heterologous strains. *W. F.*

Iyengar (M. O. T.). **Anophelines Infected with Malaria Parasites : a Further Note.**—*Records of the Malaria Survey of India.* 1934. Dec. Vol. 4. No. 4. pp. 371–372.

The author reported on a former occasion that he had found *A. jeyporiensis* James (type form) infected with malaria parasites under natural conditions in Travancore State, South India. He now amends this report and states that the infected specimens belonged to the variety *A. jeyporiensis* var. *candidiensis* Koidz. and not to the type form. *W. F.*

Howard (H. H.), Earle (W. C.) & Muench (H.). **A Method of Analysis of Field Malaria Data.**—*Jl. Amer. Statistical Assoc.* 1935. Mar. Vol. 30. No. 189A. Supplement. pp. 249–256. With 1 chart.

The data consist of (*a*) incidence of malaria, in numbers of cases per month ; (*b*) intensity of mosquito breeding, in monthly average numbers of larvae and pupae per dipping period ; (*c*) density of adult mosquito prevalence, in monthly average catches per animal-baited trap per night. The inquiry took place in Porto Rico and covers five years. A principal object of the report is to compare " inside," treated, zones with " outside " zones in six of the seven main areas of the island. The statistical method used may be illustrated on the data of monthly catches. From the experience of the five years a monthly trend was obtained and smoothed by a second order Fourier series. Then the expected values so obtained are subtracted from the individual monthly records, in order to reach indices freed so far as practicable from seasonal influence. The comparison of the residual systems of " inside " and " outside " showed a much greater rate of reduction in " inside " areas. It should be remarked that the fitted data are not actual numbers of mosquitoes caught but the natural logarithms of these numbers.

But, it might be objected that the dissimilarity of " treated " and " untreated " zones was due to the natural conditions in the latter being so unlike those of the former that no real control was provided. If this were so, then, after seasonal variations had been removed, there should be no significant correlation between fluctuations about the respective trend lines of the corresponding areas. Actually the correlation when time is held constant is increased. Further the corrrelation of different areas is insignificant (Luquillo and Santa Isabel). In 6 areas it was possible to compare " treated " and " untreated " zones with respect to the curve of captures ; in three of these the difference in favour of the " treated " is, statistically speaking, highly significant, in two others about three times the probable error of the difference, in one not significant. Only two areas permitted of comparison on the basis of cases of malaria ; in one the difference in favour of the " treated " was 2·9 times and in the other 3·7 times the probable error of the difference.

This is a carefully written and valuable piece of statistical analysis.

M. Greenwood.

Parrot (L.) & Catanei (A.). Sur les renseignements fournis par l'indice splénométrique dans la mesure du paludisme endémique. [**The Splenometric Index in Endemic Malaria.**]—*Riv. di Malariologia.* Sez. I. 1935. Vol. 14. No. 1. pp. 32–34.

The splenic index is not a very good measure of the fluctuations of endemic malaria. Though the number of palpable spleens in a community may remain approximately the same, their sizes may alter owing to a decrease or an increase in the prevalence of malaria. The author measures all spleens in finger-breadths, reckoning from the costal margin. The palpable spleens of not more than 1 finger breadth are put in category 1. Those up to 2 finger-breadths in category 2, and so on up to 5 finger-breadths in category 5. All larger spleens are put in category 6. The figure for the average sized

spleen is obtained by adding all the category figures together and dividing by the total number of enlarged spleens. The figure thus obtained, multiplied by the splenic index, gives the splenometric index. Several examples illustrating the value of this index are given. For example, the splenic index of a labour force at Mitidja was 50·9 per cent., the splenometric index was 213. After 6 months' quinine treatment there was little alteration in the splenic index, which now stood at 48·1 per cent., but the splenometric index had fallen to 110, and indicated accurately the improvement which had taken place.

W. F.

SCHEMBRA (F. W.). Zur Frage der Kriegsmalaria. [**The Question of War Malaria.**]—*Deut. Med. Woch.* 1935. June 28. Vol. 61. No. 26. pp. 1044–1045.

Account from a Berlin hospital of a case of war malaria in which fever and death from another cause occurred 17 years later with malarial parasites in the blood.

A man of 48 had malaria in Macedonia in the European War. He had relapses at irregular intervals with rigors and quinine treatment till 1926 after which the disease disappeared. In 1929 he began to have pain in the belly attributed to the gall bladder. In 1933 the pain increased and he was removed in September to hospital, where operation was refused. A few days later he began daily rigors, his blood was examined and "plasmodia of tertian type were demonstrated in several blood smears and in thick drops." Four days later he died. Autopsy showed purulent cholelithiasis and "blackish pigmentation of the liver and spleen which were both enlarged." The author says that malaria acquired later or an autochthonous infection can be excluded. Cases, it is stated, have been recorded by RUGE and by DUMOLARD & AUBRY in which tertian relapsed after 10–17 years. The bearing on the pension question is briefly discussed. [See also p. 406, above.]

A. G. B.

KELLEY (W. H.) & SYDENSTRICKER (V. P.). **Notes on Pernicious Malaria.**—*Arch. Intern. Med.* 1935. May. Vol. 55. No. 5. pp. 818–825. With 1 chart.

This report reviews observations made on patients admitted to hospital with malaria in an area along the Savannah River in Georgia. The negro is more resistant than the white man, and although the population consists of an equal number of each, many more whites than blacks were admitted.

During a period of 15 years, 700 cases of severe malaria were observed—benign tertian 198, subtertian 502. The mortality was 0·5 per cent. for benign tertian and 9·98 for subtertian. Pernicious malaria occurred in 19·34 per cent. of the subtertian cases. It was more common in negroes than in whites. About half the cerebral cases died. Haemoglobinuria occurred in 16 persons, most of whom had suffered from repeated infections. Transfusion was employed for 12 such patients, 10 of whom survived. Fourteen had taken quinine shortly before the blackwater began, but no increase in haemoglobinuria was noted in 5 of those who received blood transfusion and were subsequently treated with quinine.

W. F.

Slatineanu (A.), Nicolau (S.) & Balmus (G.). L'histopathologie du système nerveux dans le coma paludique. [**Histopathology of Nervous System in Malarial Coma.**]—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1935. Mar. Vol. 8. No. 1. pp. 5–43. With 24 figs. [47 refs.]

The authors give a comprehensive view of the work which has been published, especially as regards Dürck's nodules. They then describe very fully their own findings in a fatal case of malarial coma. The paper is illustrated by a number of drawings.

They found an acute polynuclear inflammation of the meninges with some oedema of the membranes ; swelling of the nerve cells with chromatolysis of Nissl's granules ; glial proliferation ; a parenchymatous mononuclear infiltration, which sometimes gave rise to nodules ; vascular lesions such as thrombosis, haemorrhage, and inflammation within and around the vessels ; malarial pigment in the connective tissue cells, endothelium, meninges, etc. Malarial pigment was not found within the neurones, but the authors describe a "*brown pigment*," which was very abundant there, especially in the nerve cells where it sometimes obscured their structure completely. This brown pigment contained no iron, was not doubly refractive like malaria pigment, and was neither a carotine nor a chromolipoid. Lesions in the peripheral nervous system were most marked in the spinal and plexiform ganglia. In the nerve-roots and in the nerves themselves, interstitial inflammation and perivascular changes were present.

W. F.

Tirumurti (T. S.) & Radhakrishna Rao (M. V.). **The Rôle of Malaria in the Causation of Cirrhosis of the Liver—a Preliminary Note.**—*Jl. Indian Med. Assoc.* 1935. Apr. Vol. 4. No. 8. pp. 315–317. [18 refs.]

The authors are "convinced from experience in South India that malaria *per se* is not a direct cause of cirrhosis of the liver." They have collected livers from cases of chronic malaria, and will report on them later.

W. F.

Saleun (G.) & Monier (H. M.). Renseignements et techniques particulières recueillis à l'école italienne de malariologie. [**Lessons learnt in the Italian School of Malariology.**]—*Ann. de Méd. et de Pharm. Colon.* 1934. Oct.–Nov.–Dec. Vol. 32. No. 4. pp. 472–493.

Useful notes on the testing of Paris green, reticulocytes, precipitin tests, Alessandrini's theory of macroptera and rice-fields, immunity in malaria, etc.

The authors here set out the contents of their notebooks compiled in Italy. They cover a wide range of subjects, from theories about the origin of blood corpuscles to the staining of malaria parasites. Under the heading of Paris green, they say that if this is too fine it binds into lumps and cannot be spread, while if it is too coarse it cannot be taken up by the mosquito larvae. Paris green is often adulterated with baryta. In order to detect this, put a little into a test tube containing 5 cc. of ammonia. If the Paris green is pure, the ammonia turns blue and remains clear ; but if it contains baryta,

it becomes cloudy. In order to test if the labourers are applying Paris green regularly, take 10 cc. of the water from the surface ; put it in a flask with some small pieces of zinc and a little dilute sulphuric acid ; put a piece of filter paper over the mouth of the flask, with a little powdered silver nitrate on the top of it. After a few minutes—if the water contains any Paris green—the silver nitrate becomes first yellow, then brown, and, if one adds a drop of water, black. [But all traces of arsenic disappear very quickly after dusting with Paris green.]

The method of Cesaris-Demel for the intravital staining of reticulocytes is described. The following stain is employed :—

Brilliant cresyl blue	...	...	2 gram.
Soudan III ...	...	...	4 „
Absolute alcohol	...	...	15 „

A perfectly clean slide is warmed slightly, and two drops of this stain are allowed to fall on it. This evaporates and forms a thin coloured film. A drop of the blood to be examined is taken on a cover slip, and this is dropped wet on to the coloured slide. When reticulocytes are scarce they may be concentrated by centrifuging in sodium citrate. Under the plasma in the centrifuge tube, and above the red corpuscles, comes the grey layer. In this grey layer are found, in the following order :—the white cells, the megaloblasts, the red cells containing malaria parasites. Technical notes in connexion with many other investigations are given, for example : precipitin testing of mosquito blood meals ; methods of storing live mosquitoes ; Barber's rapid method of examining salivary glands ; the mounting of mosquitoes' stomachs and salivary glands, etc. Professor Guglio Alessandrini's theory of macropteric and micropteric anopheles is mentioned. He looks upon malaria as primarily a disease of the small weak microptera which breed in the marshes where their food is protozoa. The large, strong macroptera which breed in the rice-fields and feed on nourishing plankton consisting of algae, can resist infection with the parasites of malaria. Alessandrini therefore recommends planting rice as an anti-malarial measure. The work of Schilling and Neumann in connexion with immunity in trypanosomiasis and malaria is also mentioned. Possibly the process is as follows :—antibodies are produced at the first attack and destroy all but a few parasites. Those few, resistant parasites gradually increase until they cause another attack, and produce a second lot of antibodies different from the first. Again a few parasites escape which produce a third lot of antibodies ; and so on until " the accumulation of different antibodies creates a progressive premunition." *W. F.*

van Nitsen (R.). Essai de prophylaxie rationnelle chez l'enfant indigène. [**Rational Prophylaxis in the Native Child.**]—*Bull. Méd. du Katanga.* 1934. Vol. 11. No. 6. pp. 185, 187–193.

All the native women in the Panda camp are taken into hospital for their confinements and, subsequently, they bring their babies every day to the infant-welfare centre until they are a year old. Afterwards the children are given a free meal every day in the camp canteen until they are two years old. Once a month, the blood of the children is examined by the thick film method, and those with parasites are given treatment for six days. This brings about a great improvement in the health of the children, and reduces the numbers infected with gametocytes, but it does not get rid of the children's

malaria entirely, and consequently it does not interfere with the development of immunity. The doses given were as follows :— Children up to 6 months, 5 centigrams of atebrin daily ; children from 6 months to 2 years, 10 centigrams daily. The doses of plasmoquine for the same ages were one-tenth of the doses of atebrin.

W. F.

Gaignaire. Confusion mentale, mélancolie anxieuse et mélancolie délirante curable, d'origine paludéenne. [**Mental Confusion in Malaria.**]—*Ann. de Méd. et de Pharm. Colon.* 1935. Oct.–Nov.–Dec. Vol. 32. No. 4. pp. 572–574.

The delirium of malaria usually disappears with the falling of the temperature, but the author describes three cases of pernicious malaria in natives of the Bakaka tribe, where the delirium passed into a state of mental confusion in which the hallucinations of the delirium persisted, and the patients remained in a state of terror from which they could not be aroused, but continued to groan, lament and cry out in fear. The symptoms passed off during convalescence. Three other cases from the same tribe were brought to the author suffering from mental symptoms of some months duration. Their mental state was characterized by anxiety, they groaned and lamented and accused themselves of grievous sins. Their spleens and livers were enlarged, parasites were present in the blood, and complete recovery followed anti-malaria treatment. *W. F.*

Djaparidse (P. S.). Ueber die Frage der Malariaödeme. [**Malarial Oedema.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. June. Vol. 39. No. 6. pp. 252–256.

A study of the disturbances of the water metabolism in malaria.

The author investigated the problem in 117 cases of malaria in Suchum [? Georgia, on the Black Sea]. Of the 117, 13 were infected with *Plasmodium vivax*, 79 with *Plasmodium malariae* and 25 with *Plasmodium falciparum*. Oedema occurs most frequently in cases of quartan malaria, less frequently in malignant tertian and least in benign tertian. If there are kidney lesions albuminuria with casts is present, but there may be oedema without albuminuria. The cause of oedema without albuminuria, particularly frequent in quartan malaria, is not clear and requires further investigation ; possibly endocrines may play a part. The cases of oedema without albuminuria are easily cured by quinine, and this is important in the differential diagnosis. Since cases may occur in endemic areas without showing typical signs of a malarial attack it is essential to make extensive blood investigations including the melanoflocculation reaction.

E. D. W. Greig.

Corman (A.). Hémorragie sous-capsulaire de la rate au cours d'un accès aigu de malaria. [**Rupture of the Spleen during an Acute Attack of Malaria.**]—*Bull. Méd. du Katanga.* 1935. Vol. 12. No. 1. pp. 22–25.

The rupture of an enlarged spleen during vomiting caused terrible pain and great tenderness.

The patient, a man of 32, had suffered from several attacks of malaria during the course of the two years preceding his admission to hospital. During an acute attack, he vomited violently after quinine, and, while he was retching, he was seized by a sudden pain in his left side so severe that he fainted. He was admitted to hospital with all the signs of abdominal haemorrhage and an exquisitely tender area over the left side of the abdomen, in which there was a localized area of dullness and swelling in the position of his enlarged spleen. A haemorrhage under the splenic capsule was diagnosed. He was treated with coagulant drugs and the local application of ice, and he recovered. An attack of blackwater, with malaria parasites in the blood, occurred during his convalescence and was treated with atebrin.

W. F.

Barbosa (Amando). La quinina y la atebrina en la prevención de las recrudescencias que siguen a la recurrencia de terciana benigna. (Estudio comparativo.) [**Quinine and Atebrin in preventing Recrudescences after Recurrence of Benign Tertian Malaria.**]—*Medicina Paises Cálidos.* Madrid. 1935. Mar. Vol. 8. No. 3. pp. 139–144.

The author follows James in defining a " recrudescence " as a return of fever and parasites within 8 weeks of recovery from the primary attack ; a " relapse " as a return between 8 and 24 weeks, and a " recurrence " as a return at some time later than 24 weeks (see this *Bulletin*, Vol. 28, p. 567]. He treated 49 patients suffering from benign tertian with quinine and another 49 with atebrin. In each group there were 12 adults and 37 children. The dosage of atebrin was 0·1 gm. daily for children between 6 months and 5 years ; from 5–9 years 0·15 gm., 10–12 years 0·2 gm. and over 12 years 0·3 gm. The dose of quinine was also graded, the usual dose for an adult being 1 gm.

Each patient was kept under observation for a period of two months after recovery from the recurrence. Seven recrudescences occurred among the 12 adults treated with quinine or 58·3 per cent. [The percentages are stated for purposes of readier comparison, with the known proviso of the fallacy of calculating percentages on small numbers.] There were five among adults treated with atebrin, or 41·6 per cent. Among the 37 children given quinine there were 18 recrudescences, *i.e.*, 48·6 per cent., and among those treated with atebrin 14 or 37·8 per cent. Taking adults and children together, there were 25 recrudescences among the 49 treated with quinine and 19 among the atebrin group or 51 and 38·7 per cent. respectively. In other words, atebrin is more effectual than is quinine in preventing recrudescences following recurrence of benign tertian, both in children and adults.

Again, the average period before the recrudescence in those treated with quinine was 20·4 days, in those treated with atebrin 41·7 days ; that is, atebrin delays the appearance of the recrudescence, the interval being fully double the length of that of the quinine treated group.

H. H. S.

i. Morishita (Kaoru), Miyahara (Hatsuo) & Ishioka (Hiozo). **Studies in the Treatment of Malaria XIII. Experimental Treatment with Plasmoquine and Atebrin as carried out by our APA Method.**—*Taiwan Igakkai Zasshi* (*Jl. Med. Assoc. Formosa*). 1935. Mar. Vol. 34. No. 3 (360). [In Japanese pp. 319–328. [14 refs.] English summary pp. 328–330.]

ii. ——, —— & ——. **XIV. Further Notes on the Experimental Treatment with Plasmoquine (5th Report). On a Modified Use of Plasmoquine (PQB Method).**—*Ibid.* [In Japanese pp. 338–346. English summary pp. 346–348.]

i. Twenty-one patients were given 0·3 gram atebrin and 0·03 gram of plasmoquine daily for seven days. They were kept under observation for 8 weeks, and none of them relapsed. The duration of parasites after the beginning of treatment was: benign tertian, 1 to 3 days; quartan, 1 to 4 days; crescents, 1 to 8 days; subtertian trophozoites, 1 to 3 days. The authors call this method of treatment the A.P.A. method.

ii. Twenty-two patients were treated by the P.Q.B. method which consists of 0·9 grams of quinine daily for 2 weeks, with 0·04 grams of plasmoquine in the first week. The patients were observed for 8 weeks. There was a relapse rate of 23 per cent. in benign tertian, and 15 per cent. in subtertian. *W. F.*

Ciuca (M.), Franke (M.) & Alexa (E), with the collaboration of C. Agapi, E. Pupu & E. Manoliu. Contribution à l'étude de l'efficacité thérapeutique comparée de l'atébrine seule ou associée avec d'autres produits antipaludéens dans l'infection naturelle. [**Comparative Study of Treatment by Atebrin Alone and Associated with Other Drugs.**]—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1935. Mar. Vol. 8. No. 1. pp. 111–123. With 3 figs.

The authors treated 110 patients for a period of 7 days with daily doses of one of the following :—

(*a*)	atebrin	0·30 ctgr. (? gram)
(*b*)	atebrin	0·30 + plasmoquine 0·02
(*c*)	atebrin	0·30 + quinine 0·50
(*d*)	quinine	1 gram
(*e*)	quinine	0·50 + plasmoquine 0·02

There was no apparent difference between quinine and atebrin in the treatment of the attack. Atebrin and quinine together were not superior to either drug given separately. Combined treatment with atebrin and plasmoquine often produced toxic symptoms; this combination should be used only under strict observation by a medical man. Staining of the skin in cases treated with atebrin tended to be more marked in severe cases. *W. F.*

Biggam (A. G.). **Atebrin and Malaria.**—*Jl. Roy. Army Med. Corps.* 1935. June. Vol. 64. No. 6. pp. 400–402.

Four European soldiers who had been treated with quinine and plasmoquine in the tropics, suffered from benign tertian relapses on their return to England and were treated with atebrin 0·3 grams daily for five days. Three of them relapsed in about 5 weeks and one in 14 weeks. *W. F.*

Kirilow-Drenowsky (A.). Orientierende therapeutische Versuche mit der 6-Tage-Behandlung mit Atebrin, Atebrin + Plasmochin-simplex, Plasmochin-compositum, Chinoplasmin und Chinin. [**Comparative Therapeutic Observations on a 6-Day Treatment with Atebrin, Atebrin + Plasmoquine Simplex, Plasmoquine Co., Quinoplasmoquine and Quinine.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. June. Vol. 39. No. 6. pp. 243–252.

The title of this paper indicates its scope.

The observations were made in Bulgaria in a heavily infected village in the district of Plovdiv. In May 1934 the splenic index was 82·8 per cent. and the parasite index 18·8 per cent. The treatment was begun on 27th May 1934 and ended on 5th October 1934. The nature of the infection amongst the patients was :—*Plasmodium vivax* in 78 persons, *Plasmodium malariae* in 2, *Plasmodium falciparum* in 31, and mixed in 4. The ages varied from under 1 year to over 15 years. The drugs were given in the usual doses with appropriate reductions for children of various ages. The atebrin plasmoquine-simplex combination was used in a proportion 10 : 1. Toxic symptoms were noted in some cases, chiefly abdominal pain and cyanosis of lips. As a result of the observations the author concludes that :—for a 6-day treatment the method of choice is the atebrin plasmoquine combination, it gave only a 3·7 per cent. of relapses. He puts next the atebrin treatment alone, it is remembered that young children require correspondingly higher doses. In the third place he brackets equal, quinine with a 25 per cent. relapse rate, quinoplasmoquine with 33 per cent., and plasmoquine co. with 42 per cent. of relapses. [The groups contained from 21 to 27 persons each.] *E. D. W. Greig.*

Blaze (John R.) & Simeons (A. T. W.). **Preliminary Observations on a New Soluble Atebrin Compound.**—*Indian Med. Gaz.* 1935. Apr. Vol. 70. No. 4. pp. 185–188. With 21 charts.

This is an important report on 21 cases of malaria treated very successfully with intramuscular injections of atebrin musonate.

It is a yellow, easily-soluble powder, put up in dry ampoules, each containing 0·125 grams (corresponding to 0·1 gram of atebrin dihydrochloride) to be dissolved in exactly 3 cc. of water before use. The doses recommended by the makers are 1 ampoule for intravenous injection, or 3 ampoules for intramuscular injection. According to Hecht (this *Bulletin*, Vol. 31, p. 171) atebrin is absorbed in the duodenum, and taken to the liver ; thence it is excreted with the bile back into the duodenum to pass once more back to the liver with the portal blood. According to this theory, very little atebrin reaches the general circulation until the liver has been saturated with it, and this explains why none appears in the urine until treatment has been continued for several days. Theoretically then, atebrin should act much more promptly when it is injected.

The results were as follows :—A single intramuscular injection of 0·375 grams sometimes had a remarkable effect, but a recrudescence usually occurred within a few days. Two injections given on successive days were sufficient to get rid of all asexual benign tertian and subtertian parasites within 4 days ; occasionally, parasites reappeared after a few days, but they disappeared spontaneously. The injections were painless, and there were no toxic symptoms. The intravenous route, though harmless, is not satisfactory for routine treatment. *W. F.*

Slatineanu (A.) & Sibi (M.) with the collaboration of M. Francke, E. Veit, E. Lupu & Z. Paraschivescu. Exploration fonctionnelle du foie et du rein dans le paludisme, avant et après traitement à l'atébrine pure ou combinée avec plasmoquine ou quinine. [**The Liver and Kidney in Malaria and after Atebrin Treatment.**]—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1934. Dec. Vol. 7. No. 4. pp. 529–543. [32 refs.]

The yellow colouration of the skin produced by atebrin is a danger sign, and patients showing it should be watched carefully. It appears to be associated with defective action of the liver and kidneys. Atebrin should not be employed except under medical supervision. Before treatment, a transitory hepatic insufficiency was found in all the 60 cases of malaria examined ; it was less marked in benign tertian ; acidosis was associated with it in many cases. No great reduction of chlorine or great azotaemia were found. A moderate renal insufficiency was found in subtertian and quartan. *W. F.*

Soni (R. L.). **A Note on Yellow Discoloration in Atebrin Therapy.**—*Indian Med. Gaz.* 1935. Apr. Vol. 70. No. 4. pp. 211–212.

Atebrin pigmentation never occurs before the third day. Slow excretion and cumulation are important factors, but constipation, intercurrent infections, etc., also modify the intensity and duration of the discolouration. The author gives details of a case in which pigmentation persisted for three months, and he ascribes the unusually long duration to a streptococcal infection of the throat from which the patient was suffering. *W. F.*

Storm (C. J.). Ueber die Anwendung des Suprarenins bei intravenöser Injektion von Atebrin im Affenversuch. [**Use of Adrenalin in Intravenous Injections of Atebrin to Monkeys.**]—*Klin. Woch.* 1935. May 25. Vol. 14. No. 21. pp. 756–758. With 3 text figs. [13 refs.]

An experimental study on the control by adrenalin of the toxic symptoms produced by intravenous injections of atebrin.

The author carried out his experiments on monkeys. Intravenous injection of atebrin has a marked effect on the circulation evidenced by a pronounced drop in blood pressure, also by irregularities in the rhythm of the pressure curve due mostly to extra systoles. The author showed by his experiments that this fall in pressure could be prevented by adrenalin and for this and other reasons he recommends the use of adrenalin with intravenous injections of atebrin.

E. D. W. Greig.

i. Hecht (Gerhard). Experimentelle Untersuchung von Zirkulationsstörungen durch Plasmochin und Atebrin. Erwiderung auf die Arbeit von de Langen und Storm. [**Experimental Investigation of Circulatory Disturbance by Plasmoquine and Atebrin. Reply to de Langen and Storm.**]*—*Klin. Woch.* 1935. Vol. 14. pp. 714–716. [16 refs.]

ii. Eichholtz (F.). Bemerkungen zur Arbeit von de Langen und Storm. [**Notes on the Work of de Langen and Storm.**]—*Ibid.* pp. 716–718.

[The opportunity—denied to most European laboratories—of using monkeys as test animals is fully taken advantage of by workers in

*de Langen & Storm's article was reviewed on page 418.

the Dutch East Indies and there is little doubt of the importance and utility of such experiments, especially in pharmacology. It was, however, only to be expected that emphasis of the complications which may follow the use in man of the most important antimalarial synthetic drugs of recent times, atebrin and plasmoquine, based on monkey experiments, should elicit a reply from those who have used mainly the smaller laboratory mammals for test. The subject is a very important one for tropical practitioners and we may, without passing any judgment on the controversy, extract the opinions of those who are well qualified to express them.]

i. Hecht questions the claim that monkeys are ideal test animals and attributes the supposed great susceptibility of the monkey heart to atebrin as due rather to the ill-advised perfusion method employed. Again, he considers that parenteral injection of a test drug cannot furnish a criticism of its suitability for oral administration. This is especially the case for intravenous injection. He is convinced too, that intramuscular injection in monkeys has just the same action as in cats. With these latter animals he could discover no effect upon respiration and circulation of even 20 mgm. atebrin per kgm. by intramuscular injection, although a negative variation of blood pressure could be obtained with a dose intravenously of 2 mgm. per kgm. Such an effect then could only be expected in man by intravenous injection. There is, however, no indication at all for intravenous injection of plasmoquine for its gametocidal effect. There are rare occasions, however (malarial coma) where urgency demands immediate action upon malarial schizonts and here the choice must lie between intravenous administration of atebrin or quinine. Tropical practitioners have already used the tablets of atebrin, intended for oral administration, for this purpose and have found that intravenous doses of 0·2 gm. atebrin—corresponding to 3 mgm. per kgm.—have been seldom followed by any complication. Evidently the dose recommended for intravenous injection is to be of the order of 0·1 gm. Such a dose would seem to come within the limit of safety as laid down by DE LANGEN for man. Such a man, " of 50 kilogm., in good bodily condition, with a blood pressure not lower than 100 mm. could probably stand an intravenous dose of 200 mgm. atebrin." The position reduces to this, that both atebrin and quinine have their dangers, when used by intravenous injection and the choice is left by the author to the practitioner whether he will select for intravenous inoculation an intravenous dose " of 0·1 gm. atebrin (which may be repeated 2 or 3 times without danger, as is shown by animal experiment, at intervals of an hour) or an effective dose of quinine."

ii. The main complications to be expected from the action of plasmoquine are disturbance of cardiac rhythm and formation of methaemoglobin. But in the case of man very much smaller therapeutic doses are necessary than are capable of producing these effects, especially the doses that are used at the present time, which have diminished from the original 0·06 to 0·02 or 0·03. The author is not in favour of the combination of adrenalin, which has its own dangers, with plasmoquine nor yet of combining quinine and plasmoquine in intravenous injection. *W. F. Harvey.*

Wats (R. C.) & Ghosh (B. N.). **Quantitative and Qualitative Methods for Detection of Atebrin in Urine.**—*Records of the Malaria Survey of India.* 1934. Dec. Vol. 4. No. 4. pp. 367–370.

The technique of the qualitative test is as follows ; those wishing to carry out quantitative tests should consult the original :—

" (1) About 100 c.c. of the urine containing atebrin are rendered alkaline with 10 gm. of potassium carbonate, and shaken with 20 c.c. of amyl alcohol in a glass cylinder.

" (2) The supernatant alcohol layer is poured off from the top, and, if turbid, is washed with a saturated aqueous solution of potassium carbonate.

" (3) The presence of atebrin would be evident from the typical yellow colour imparted to amyl alcohol, and can be confirmed in the following way. With a convex lens the bright sunlight is focused against a black background and the tube containing the extracted amyl alcohol interposed in a slanting position between the lens and its focus. A distinctly green fluorescence is noticeable in the beam of light, especially on moving the lens parallel to the tube. It should be distinguished from the faint blue fluorescence sometimes caused by the solution of urobilin in amyl alcohol.*

" The green fluorescence, mentioned above, is quite distinctly shown in an amyl alcohol extract containing atebrin in dilutions up to 1 in 2,000,000. This last would correspond to the presence of atebrin in a dilution up to 1 in 10,000,000 in the urine tested." *W. F.*

Blackie (W. K.). **A Fatal Case of Plasmoquine Poisoning.**—*South African Med. Jl.* 1935. Mar. 9. Vol. 9. No. 5. pp. 147–148.

" The tragic termination of this self-treated case points clearly to the need for medical supervision in all cases of plasmoquine therapy."

The deceased had twice suffered from blackwater, and each time the attack had followed a small dose of quinine. Three days before his death, he felt seedy and obtained plasmoquine and atebrin from a chemist. In the following 24 hours, he took 0·6 gm. of atebrin and 0·03 gm. of plasmoquine, after which he complained of a tightness about the throat and respiratory distress. He continued with the drugs and, on the second day, he took the same doses as on the first. He then complained of griping pains in the abdomen, together with difficulty in breathing, swallowing and speaking. His temperature had risen to 102°F. and his lips were blue. He died on the following morning. No signs of recent malaria were found post mortem. Cyanosis was present in the finger-nails, the ears, lips, gums and palate. The kidneys were intensely congested and swollen ; they presented the appearance of acute haemorrhagic nephritis. The liver was soft, " suggestive of . . . parenchymatous necrosis." The highly acid urine contained methaemoglobin, granular casts, granular débris, and numerous leucocytes. *W. F.*

Hicks (E. P.) & Chand (Diwan). **The Relative Clinical Efficacy of Totaquina and Quinine.**—*Records of the Malaria Survey of India.* 1935. Mar. Vol. 5. No. 1. pp. 39–50.

The authors found that quinine and both types of totaquina were

* " We have found that if one drop of pure sulphuric acid be added to every c.c. of the amyl alcohol extract, and the mixture be heated in a boiling-water bath for 3 minutes, the blue fluorescence due to urobilin is eliminated. The specimen should, however, be examined while still hot, as some turbidity appears on cooling.

" The addition of quinine salts, salicylates, caffein, plasmoquine or iron salts to the urine has not been found to interfere with the green fluorescence characteristic of the amyl alcohol extract containing atebrin."

of equal efficacy in the immediate cure of malaria, and that there was no appreciable difference in their toxicity.

They treated 210 prisoners suffering from benign tertian and 158 suffering from malignant tertian. The drugs used were (*a*) quinine ; (*b*) totaquina Type 1 which contained 32 per cent. quinine and 11 per cent. cinchonine ; (*c*) totaquina Type II which contained 19 per cent. quinine and 20 per cent. of cinchonine. The doses were 0·6 gm. daily per 70 kgm. of body weight in benign tertian, and 1·2 gm. daily in subtertian. The drugs were given in tablets. The patients had been exposed to malaria all their lives. The mean duration of parasites, under treatment with any one of the three drugs, was less than 1·5 days ; the mean duration of fever was less than 2 days. Parasites and fever disappeared rather more quickly with totaquina Type II ; " in most cases the differences between the drugs are small and are within the limits of error due to random sampling." The authors " suggest that a dose of 1·0 gm. or 15 grains once daily for 3 or 4 days would be suitable for the routine treatment of rural populations in the Punjab. This should be large enough to prevent the majority of deaths and to remove the clinical symptoms, which is all that is demanded by such populations." [See pp. 114 and 410, above.]

W. F.

PÂRVULESCU, CONSTANTINESCO (N.) & BOERIU (V.). Efficacité comparée du totaquina dans le paludisme humain (infection naturelle). [**Totaquina in Malaria. Comparative Worth.**]—*Arch. Roumaines Path. Expérim. et Microbiol.* Paris. 1934. Dec. Vol. 7. No. 4. pp. 523–528.

Comparative tests were made with two samples of totaquina, Type I ; with two samples of totaquina, Type II ; and with quinine sulphate. The tests were made upon 213 young soldiers who were in hospital suffering from malaria. Benign tertian patients were given 0·6 gm. (9 grains) daily for 5 days ; subtertian and quartan cases were given 1·2 gm. (18 grains). These small doses were employed in order to bring out the difference in the efficiency of the several drugs ; when double these quantities were given they were all equally effective. The results showed that a Type I totaquina, or a Type II totaquina which has been brought up to the same standard, acted as well as quinine ; but, in the small doses used, a Type II totaquina, of which more than 50 per cent. of the alkaloids consisted of cinchonine, was less efficient.

W. F.

PINELLI (Luigi). La terapia cacodilica ad alte dosi nella malaria acuta e cronica. [**Sodium Cacodylate in the Treatment of Malaria.**] —*Riv. di Malariologia.* Sez. I. 1935. Vol. 14. No. 2. pp. 136–145. French summary.

The author states that sodium cacodylate causes no inconvenience, has no effect on the temperature nor any destructive action on the asexual forms. The enlargement of the spleen is little if at all reduced and that little only if the enlargement is recent. It does however improve the general condition, especially in chronic malaria, increases the body weight, restores the blood to normal and effectively enhances the action of the quinine.

Fifteen patients suffering from acute malaria, primary or relapse, and 20 suffering from chronic forms of the infection were treated with large

doses. The drug was made up of a strength of 0·25 gm. in 1 cc. with distilled water. In acute cases 0·3–1·5 gm. were given daily for 10 days, either intramuscularly or intravenously. In chronic cases the course was spread over 20–30 days, including days of intermission in administration; thus: For the first two days 2 cc. morning and afternoon = 1 gm. of the drug in the day. This was followed by two days' rest. On the next three days 2 cc. were injected in the morning, at midday and in the evening, *i.e.*, 6 cc. or 1·5 gm. of the drug; 3 days' rest. For the next five days 4 cc. morning and evening = 2 gm. in all, and after another 5 days' rest, injections daily for 5 days of 4 cc. morning, midday and evening. [The author calls this a total of "2·5 gm. of cacodylate in the day," but 12 cc. would contain 3 gm.] At the morning dose 1·4 gm. quinine [? salt] is given *per os*. Two courses with an interval of 20 days suffice to cure. *H. H. S.*

SAUTET (Jacques). Contribution à l'étude du paludisme chez les enfants. Les traitements nouveaux. [**Treatment of Malaria in Children.**]—*Rev. Méd. et Hyg. Trop.* 1934. Nov.–Dec. Vol. 26. No. 6. pp. 257–261.

The author gives a table of the doses of acridine and quinoline derivatives recommended for children.

He stresses the importance of treating children, because they are the chief reservoirs of infection. He begins treatment either with quinine, or with one of the acridine derivatives, *i.e.*, with atebrin or quinacrine which are identical substances. A useful method for children is to conceal the tablet in a raisin. The doses recommended are:—

0 to 6 months ...	...	quinine is preferable.
6 months to 1 year	...	0·025 gram acridine derivative daily for 4 days.
1 year to 2 years	...	0·05 ,, ,, ,,
2 years to 4 years	...	0·10 ,, ,, ,,
4 years to 8 years	...	0·15 ,, ,, ,,
8 years to 10 years	...	0·25 ,, ,, ,,
10 years to 15 years	...	0·30 gram acridine derivative daily for 5 days.

The daily amount should be given in 2 or 3 doses.

This treatment should be followed by treatment with one of the quinoline derivatives—plasmoquine (Bayer), rhodoquine (Poulenc-Rhone), plasmoquine (Russian)—in order to destroy the gametocytes. These drugs are easy to give because they are not bitter like the acridine derivatives, but they are toxic. The doses recommended are:—

0 to 6 months ...	...	0·0025 gram.
6 months to 2 years	...	0·0050 ,,
2 years to 4 years ...	...	0·0075 ,,
4 years to 8 years ...	...	0·0100 ,,
8 years to 10 years	...	0·0150 ,,
10 years to 15 years	...	0·0200 ,,

These doses are given twice a week for 6 months. *W. F.*

PITTALUGA (G.). Die Behandlung der Malaria. (Zusammenfassung der Erfahrungen spanischer Malariologen.) [**Treatment of Malaria in Spain.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. July. Vol. 39. No. 7. pp. 291–296.

The experiences of Spanish malariologists in the treatment of malaria.

The problems with which they had to deal were :—1. The treatment of acute primary cases of the three types. 2. The treatment of relapses of long and short duration. 3. The treatment of chronic and latent cases with general and visceral symptoms, splenomegaly, anaemia, etc. 4. The treatment of abnormal forms of the disease, mixed infections, blackwater fever, quinine idiosyncrasy.

The author considers the most satisfactory scheme of treatment is a 7-day treatment with atebrin in the usual doses followed by a course of plasmoquine. At end of this course an after treatment with quinine and arsenic for 14 days is advised. He recommends the parenteral treatment with adrenaline as a supplementary therapy for the asthenia which accompanies many cases of malaria. *E. D. W. Greig.*

Alessandrini (G.). Nuove vedute sulla biologia dei parassiti malarigeni. *Atti V. Congr. Naz. Microbiol., Cagliari 27–31 Maggio 1934.* pp. 17–37. [See this *Bulletin*, Vol. 30, p. 734.]

Arima (I.). Beitrag zur Malaria-Serumreaktion (Melanoflockulation).—*Fukuoka Acta Med.* (*Fukuoka-Ikwadaigaku Zasshi*). 1935. June. Vol. 28. No. 6. [In Japanese. German summary pp. 61–62.]

Baldi (Americo). Malaria autoctona nel comune di Pistoia. Nota preventiva.—*Riv. di Malariologia.* Sez. I. 1935. Vol. 14. No. 1. pp. 42–44. French summary (6 lines).

Benarroch (E. I.). A propos de la réaction de Henry pour la diagnostic du paludisme.—*Riv. di Malariologia.* Sez. II. 1934. Vol. 13. No. 6. pp. 329–341.

Bourgin (P.). Un cas d'hémorragie intestinale palustre à Soctrang.—*Bull. Soc. Méd.-Chirurg. Indochine.* 1935. Feb.–Mar. Vol. 13. No. 2. pp. 139–141.

Canavan (Wm. P. N.). Present Status of Malaria in Oklahoma.—*Amer. Jl. Trop. Med.* 1935. Mar. Vol. 15. No. 2. pp. 225–230. With 3 figs.

Chini (Virgilio). Sindrome nervosa extrapiramidale di natura malarica.—*Policlinico.* Sez. Med. 1935. July 1. Vol. 42. No. 7. pp. 389–404. [32 refs.]

Copeland (A. J.). Malaria and Racial Extinction. [Correspondence.]—*Lancet.* 1935. June 22. p. 1472.

Ficacci (Luigi). Emoglobinuria da plasmochina.—*Policlinico.* Sez. Prat. 1935. Jan. 28. Vol. 42. No. 4. pp. 136–139.

Greenfield (Gregor). Ein Fall von Malaria mit Mastitis.—*Arch. f. Schiffs- u. Trop.-Hyg.* 1935. Aug. Vol. 39. No. 8. pp. 347–348. [See this *Bulletin*, Vol. 13, p. 72.]

Hauer (August). Ueber Chininintoxikation und Chininidiosynkrasie.—*Deut. Med. Woch.* 1935. Mar. 1. Vol. 61. No. 9. pp. 332–336. [22 refs.]

Henry (A. F. X.). Floculation mélanique et instabilité sérique. Courbes de malariafloculation. Le clavier sérologique du paludéen.—*C. R. Soc. Biol.* 1935. Vol. 119. No. 21. pp. 597–600.

Kikuth (Walter). Die experimentelle Chemotherapie der Malaria.—*Deut. Med. Woch.* 1935. Apr. 12. Vol. 61. No. 15. pp. 573–577.

Kikuth (W.) & Schönhöfer (F.). Erwiderung auf vorstehende Arbeit von Kritschewski und Pines.—*Klin. Woch.* 1935. Jan. 5. Vol. 14. No. 1. p. 24.

Kritschewski (J. L.) & Pines (A. I.). Die Wirkung der Chinolinderivate auf Gametocyten von *Plasmodium praecox*. Eine Erwiderung auf den Artikel von W. Kikuth und W. Schönhöfer " Zur Frage der Gametocytenwirkung des Plasmochins " in Jg. 1934, Nr. 24 dieser Wochenschrift.—*Klin. Woch.* 1935. Jan. 5. Vol. 14. No. 1. pp. 23–24.

DE LANGEN (C. D.) & STORM (C. J.). A Comparative Clinical and Experimental Study of the Action of Quinine, Plasmoquine and Atebrin.—*Meded. Dienst d. Volksgezondheid in Nederl.-Indië.* 1935. Vol. 24. No. 2. pp. 27–56. With 22 figs. [31 refs.]

[This paper is the same as that noticed on p. 418 *ante*, with slightly different title.]

LINDBERG (K.). Notes on Malaria on the Barsi Light Railway (Deccan).—*Records of the Malaria Survey of India.* 1935. Mar. Vol. 5. No. 1. pp. 51–95. With 3 graphs. [10 refs.]

LIU (Lansing S.). The Prevalence of Malaria among Railroad Workers at the Hunan Kwantung Border.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 159–164. With 1 map. [12 refs.]

LIU (K. B.). Observations on the Treatment of Malaria with Atebrin, Malarcan, Totaquina, and Quino-Plasmoquine.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 299–302.

MESNARD (J.) & TOUMANOFF (C.). Contribution à l'étude des habitudes trophiques des anophélines de la Cochinchine.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 53–63. [10 refs.]

MITCHELL (Edward Clay) & GOLTMAN (David W.). Clinical Results in the Treatment of Malaria with Combinations of Quinine, Atabrine and Plasmochin during Four Years' Experience.—*Southern Med. Jl.* 1935. June. Vol. 28. No. 6. pp. 536–542.

MORIN (Henry G. S.). Sur l'activité prophylactique du service antipaludique des Instituts Pasteurs d'Indochine.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 107–128. With 4 figs., 1 map & 2 charts.

MORIN (Henry G. S.) & CARTON (P.). De l'influence des facteurs climatiques sur la répartition de l'endémie palustre en Indochine.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 145–158. With 1 chart.

MORISHITA (Kaoru). On *Anopheles* (*Myzomyia*) *indefinitus* (Ludlow, 1904) in Formosa. Adjustment of *A. formosaensis* II, *A. rossii* and *A. vagus* Problem. —*Taiwan Igakkai Zasshi* (*Jl. Med. Assoc. Formosa*). 1935. May. Vol. 34. No. 5 (362). [In Japanese pp. 558–576. With 1 fig. [24 refs.] English summary pp. 577–578.]

MÜHLENS (P.) Are the Sequelae of Malaria contracted on Active Service Still Prevalent?—*Jl. Roy. Army Med. Corps.* 1935. Apr. Vol. 64. No. 4. pp. 247–249.

PRADO (Alcides) & GODINHO (Raul). Provavel caso autochtone de impaludismo registado en S. Paulo.—*Ann. Paulist. Med. e Cirurg.* 1935. Apr. Vol. 29. No. 4. pp. 295–297.

RAMOS (Jose). Algunas consideraciones referentes a la marcha del paludismo en San Fulgencio (Alicante).—*Rev. San. e Hig. Pública.* 1935. July. Vol. 10. No. 7. pp. 33–43. With 8 graphs.

ROBIN (L. A.). Observations sur la prémunition antipalustre chez l'Annamite adulte.—*Far Eastern Assoc. Trop. Med. Trans. Ninth Congress, Nanking, China, 1934.* Vol. 2. pp. 129–144. With 3 graphs.

ROUKHADZE (N. P.). [The Deflection of *Anopheles maculipennis* by Domestic Animals and its Significance in the Prophylaxis of Malaria.]—*Med. Parasit. & Parasitic Dis.* Moscow. 1935. Vol. 4. No. 1–2. [In Russian pp. 121–125.]

RUSSELL (Paul F.) & BAISAS (Francisco). A Practical Illustrated Key to Larvae of Philippine Anopheles.—*Philippine Jl. Sci.* 1934. Dec. Vol. 55. No. 4. pp. 307–336. With 33 plates & 5 figs. [14 refs.]

SEREFETTIN (Osman). Atropische Cirrhose malarischen Ursprunges.—*Wien. Klin. Woch.* 1935. Apr. 12. Vol. 48. No. 15. pp. 466–468.

SHIPTON (Eva A.) & VICKERY (Donald). A Case of Congenital Malaria.—*Med. Jl. Australia.* 1935. May 25. 22nd Year. Vol. 1. No. 21. pp. 655–656.

Stejskal (Karl). Kommen heute noch Kriegsmalariafolgen vor ?—*Wien. Klin. Woch.* 1935. Apr. 26. Vol. 48. No. 17. p. 532.

Tillema (S.). Malaria te Loa Koeloe. De lichamelijke weerstand als factor bij de malariabestrijding.—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1935. Apr. 2. Vol. 75. No. 7. pp. 574–576.

Trensz (F.). Le rôle du système réticulo-endothélial dans le mécanisme de la sérofloculation palustre de Henry.—*Bull. Soc. Path. Exot.* 1935. Mar. 13. Vol. 28. No. 3. pp. 174–176.

REVIEWS AND NOTICES.

CALCUTTA. **Twelfth Conference of Medical Research Workers held at Calcutta from 26th November to 1st December, 1934.**—pp. iii + 210. 1935. Simla: Govt. of India Press.

A congress of workers, in which those workers not only submit reports of progress but make an appeal to their fellows for their approval of the continuance of the work, has a special interest of its own. The business of the congress is, of course, not simply budgetary, for it affords an opportunity for workers to meet and discuss their researches. As in previous conferences the range of the subject matter is very wide; it covers all those diseases, malaria, cholera, plague, rabies, leprosy, kala azar and others which have some title to be called the chief diseases of India, together with extremely interesting references to nutrition research, tuberculosis, the extent and intensity of extreme ultra-violet solar radiation, maternal mortality, yellow fever and cancer.

A new decision has been come to regarding the status of the Indian Research Fund Association which is now to be a local body *not* administered by the Government of India. This seems calculated to give even greater freedom to the medical control of the work done than hitherto. The conference although largely composed of government officials appears to have opportunity for fairly free speech, as is evidenced by the occasional incorporation of criticisms of government medical policy.

A series of 55 appendices contain for the most part the accounts of special research work. Cholera research is one of great importance. It is rather startling here to find an expression of doubt of the value of statistical analysis of figures for the effect of bacteriophage in the prevention of cholera. This however, presumably, is not a reflection on what is generally regarded as the only means available for dealing with the case of prophylaxis or treatment in the field but to the difficulty of obtaining reliable statistics. The committee on this subject, too, has evidently not been entirely satisfied with certain of the statistical data. One notes with satisfaction a preliminary, although rather disappointing, attempt to put the question of efficacy of bacteriophage to rigorous experimental animal test with the use of *Past. pestis* as the test bacterium. Statistical data should be obtainable in laboratory controlled trials even though the persistent and distant carriage of bacteriophage does prove a considerable difficulty. A very interesting study of "carrier" cholera vibrios is presented, which should yield results of considerable epidemiological and public health importance. It deals with such subjects as the virulence of and protection afforded by carrier vibrios and the serological differentiation of vibrios. In the case of plague vaccine research many points might be noticed if space allowed. Since the beginning of the year a change has been introduced in the preparation of Haffkine vaccine. The seed is now obtained from blood obtained from human cases, instead of, as formerly, by passage of cultures through Madras rats (non-immune house rats).

Mention is made in one of the later appendices of investigation into the possibility of utilizing the solar rays for bactericidal purposes. That subject has only been dealt with in India in a very restricted sense and might yield important results especially if it were conjoined

with the suggestion here made of the use of the sun's rays prophylactically and therapeutically. Another announcement which excites interest is that " work on anaemias of pregnancy will once again be taken up." These anaemias are not special to India but the material available for trial of therapeutic measures is evidently superabundant there. Quite recently discussion has arisen over the relative values of quinine, atebrin and plasmoquine in malaria. In British India just as in Netherlands India the monkey is available as a supremely useful test animal and we have in this report some reference to " experimental work with *Plasmodium knowlesi* infection in *Silenus rhesus*."

In conclusion of this very brief and inadequate summary we may refer to the survey of cancer in India and to the statements " that malignant disease is not uncommon in India " and, " that the incidence of cancer in India stands at a figure not far removed from its incidence in the West." Much important matter for consideration and digest should emerge from a thorough going study of cancer data in India, some of which is already presented here ; explanations, for example, of why buccal cancer and skin cancer fall heavier on the male than the female and on the Muslim than the Hindu. The duration for which the betel quid is retained in the mouth and greater exposure to direct sunlight are mentioned as factors. *W. F. Harvey.*

CALCUTTA. **Annual Report of the Calcutta School of Tropical Medicine and the Carmichael Hospital for Tropical Diseases 1934** [CHOPRA (R. N.), Officiating Director].—182 pp. With 4 charts & 4 plates. 1935. Alipore : Bengal Govt. Press.

The annual report of the Calcutta School of Tropical Medicine is one of those useful and interesting publications which to some extent serves the purpose of a year book on the subject. Its matter may not be quite co-extensive with the entire field but covers a considerable part of it and especially the part which deals with important current research. A survey of the whole work is presented by the Director of the School and this serves to focus one's attention on the worker, his work, the objects he has in view and the results which he has attained. It forms a most useful introduction to the more specialized sectional reports which follow. Constant reference is made to the Carmichael Hospital for Tropical Diseases, which is attached to the school definitely for teaching purposes. The ability to call up from a waiting list a series of illustrative cases throughout the session of the school must add enormously to the impressiveness of the teaching given and it is no wonder that the Superintendent of the Hospital is moved " again to draw the attention . . . of medical practitioners to the fact that the Carmichael Hospital for Tropical Diseases is *not* an emergency hospital."

An interesting commentary on the modern methods of identification of bacteria or of bacterial infection is afforded by the remark of the Professor of Bacteriology, when he says that " the old routine Widal reaction for enteric infections, when three antigens only were employed, has been discarded and has been replaced by a fuller method employing five suspensions for the detection of flagellar agglutinins as well as four antigens for the detection of somatic agglutinins." Under the implied heading of dysentery, or dysentery-like diseases, where the patients were suffering from vague abdominal symptoms only and very few from

acute bacillary dysentery, there is an interesting table of the species and frequency of the organisms isolated. Shiga and Flexner bacteria were isolated only once and 28 times respectively as compared with 167 and 100 for *Bact. pseudocarolinus* and *Bact. asiaticus*. The number of specimens (3,675) examined corresponded to 1,220 patients. Other striking numbers in this analysis were 0, 131, 52 and 100 for Sonne, *Bact. alkaligenes*, *Ps. pyocyanea* and " other non-lactose fermenters " respectively.

Cholera research continues vigorously, as it should, in the reputed home of Asiatic cholera. Cholera phages have reached the letter L in their progress down the alphabet and, in addition to these, 15 different groups of vibriophages have been separated out. It is a new announcement to find that " what is required in a disease like cholera is not only something like bacteriophage that will destroy the vibrio, but something that can neutralize the toxins and thus act directly on the cause of the lesions. This agent would be a potent cholera antitoxin and this, combined with bacteriophage, would constitute the ideal method of treatment of cholera." Again the searcher after scientific truth in the field of therapy is puzzled by the remark that " the value of bacteriophage, if any, is very limited in the treatment of cholera." It is interesting to note—especially in its bearing on the view, which seems to have been definitely rejected in Europe, that true cholera vibrios may undergo transmutation—that " during the decline of the epidemic and the inter-epidemic period cases of clinical cholera passing non-agglutinating vibrios are far more frequent than during the epidemic period."

One affection in India which has, perhaps, not received the attention that it deserves from the research worker is " hill diarrhoea." There seems some prospect, according to this report, of this omission being remedied. It may not really be an omission, when one looks back on the researches which have already been carried through. This may be seen from the remarks that : (1) " The malady is popularly known as ' hill diarrhoea ' and in some instances the disease has received specific names such as ' Poonaitis ' . . . , ' Simlitis ' and so on " and (2) " The results obtained indicate that a great many of the bowel disturbances in Darjeeling are due to micro-organisms both bacillary and protozoal, well recognized as causative agents of dysentery."

Dengue is a disease of which much is known, but much still remains unknown. Its insect vector is now well established and it is a very important disease in the commercial life of Calcutta. Here we learn that, " The maximum peak of *Aëdes aegypti* breeding is in July and August ; and this corresponds to the maximum intensity of fresh infections with dengue (August and September). . . . This accounts for the devastating epidemics of dengue which so often sweep the city and cause enormous financial loss."

In amoebiasis research has been made into the value of carbarsone, an organic arsenic compound and it would seem to be as effective as emetine without the untoward toxic action of the latter. Its arsenic content would seem also to be beneficial to the general condition of the patient.

Monkeys, as subjects of malarial infection, are certain to lend themselves to the elucidation of many still unsettled problems in malaria. An important finding in this connexion is the discovery that the " Singapore " monkey (*Silenus irus*), a macaque, appears to be almost always infested with latent malaria of its own, whereas the " Bengal "

monkey (*S. rhesus*), also a macaque, " appears to be entirely free from any naturally acquired malaria of its own . . . but extremely susceptible to monkey malaria by inoculation."

So we might continue to make interesting quotations from the several special reports but considerations of space must limit us to two more only, from the report of the Professor of Pharmacology. Daboia and other snake venoms are now receiving attention for their therapeutic possibilities. Investigation has shown that " Daboia venom has a marked tendency to produce thrombosis and gangrene at the site of the bite and death is due to secondary shock. . . . That the nervous centres are not much affected is shown by the fact that in decerebrated animals exactly the same results are produced. . . . The symptoms of shock in daboia poisoning are not due to reflex impulses but are due to the local dilatation of the capillaries of the splanchnic area."

The administration of opium dope to infants, which is not unknown in this country, is treated under the heading of " Drug Addiction Inquiry," although the addiction in this case must be entirely involuntary and, as such, somewhat of a contradiction in terms. " Habitual administration of opium to infants . . . has been prevalent in India for many centuries. . . . The custom . . . has greatly declined during the last two or three decades. . . . The main reason for administering the drug is economic, the drug being given to keep the children quiet so as to allow the mother to carry out her work, whether in the factory or the field, unhampered. . . . The drug is usually discontinued when the child attains the age of 2 to 3 years. . . . The dose varies from $\frac{1}{8}$ to 3 grains daily. . . . The drug affects the child's health adversely and hinders growth." *W. F. Harvey.*

FAR EASTERN ASSOCIATION OF TROPICAL MEDICINE. **Transactions of the Ninth Congress held in Nanking, China, October 2–8, 1934.** [Edited by WU LIEN-TEH, Director, National Quarantine Service & C. Y. WU, Senior Medical Officer, National Quarantine Service.] —Volume I. pp. xiv + 790. Volume II. pp. x + 1,000. With numerous plates, charts & tables. 1935. Nanking: The National Health Administration. [£2 nett per set of two vols.]

These Transactions, occupying two volumes of 790 and 1,000 pages respectively, appear within six months of the close of the Congress and this in the Far East where we do not expect to find the hustle of the West. This is attributable to the energy of the Editors, Drs. Wu Lien-Teh and C. Y. Wu, and to the fact that no proofs were sent to the authors of papers. The scientific matter is arranged alphabetically by subjects, Vol. I comprising from Bacteriology to Leprosy and Vol. 2 from Malaria to Surgery. It is not necessary here to say anything about the contributions since they will be noticed in their appropriate places, but it may be noted that under malaria there are 20 papers, under helminthology 15, leprosy 12, plague and cholera 4 each, kala azar 4 ; there are nearly 200 in all.

It is of interest to note what Resolutions were passed, for these are an Index to those diseases or conditions which are either not yet fully elucidated or are inadequately controlled. One stresses " the urgent advisability of adopting practical measures for the rat-proofing of vessels " and calls attention to how far similar methods could be

employed to keep railway systems free from rat infestation, and to the need for study of rodents other than the rat as plague hosts.

A cholera Resolution demands further investigation of " carriers " in the Far East, statistically controlled tests of protection conferred by anticholera vaccine, studies of the relation between the cholera and allied vibrios, and more exact information about the epidemic and endemic areas of cholera in the Far East. The malaria Resolution is reproduced elsewhere.

The volumes close with an Index of Authors and Subjects and the editors and all concerned may be congratulated on the result of their labours. *A. G. B.*

i. Bibliography of Helminthology for the Year 1933. (Compiled by A. Walton from Titles selected by R. T. Leiper.)—101 pp. 1935. July. St. Albans: Imperial Bureau of Agricultural Parasitology. [8*s*.]

ii. Stiles (C. W.) & Baker (Clara Edith). **Key-Catalogue of Parasites Reported for Carnivora (Cats, Dogs, Bears, etc.) with their Possible Public Health Importance.**—*Nat. Inst. Health Bull. No. 163.* Wash. (Continuation of Hyg. Lab. Bull. Ser.). 1934. Dec. pp. ii+913–1223. 1935. Washington: U.S. Govt. Printing Office.

i. This issue of the Bibliography gives the titles of 1,367 helminthological papers from 471 journals and of 25 monographs, dissertations and books on helminthology traced by the Bureau as issued during 1933. A " Publisher's Note " in the form of a loose printed slip states that—" From 1934 (Vol. III) ' Helminthological Abstracts ' will be published by the Imperial Bureau of Agricultural Parasitology. The ' Bibliography of Helminthology ' will no longer be issued separately but will be combined with it under the title ' Helminthological Abstracts incorporating Bibliography of Helminthology'."

[As the first four parts of Vol. III of " Helminthological Abstracts " have already appeared under their original unexpanded title and the publisher's imprint of the Institute of Agricultural Parasitology, the change now announced must in some way be made to operate retrospectively. " Helminthological Abstracts " edited by Professor Leiper, first appeared in 1932 as a Supplement to the *Journal of Helminthology* published by the Institute of Agricultural Parasitology of the London School of Hygiene and Tropical Medicine. Volume I—the only volume so far completed—gives a résumé of the helminthological literature of 1932 and reviews 891 of 1,304 papers traced by the associated Imperial Bureau of Agricultural Parasitology for that year. Volumes II and III which are concerned with the literature of 1933 and 1934 respectively, still await the issue of their concluding parts and indexes. The first part of Vol. IV, dealing with the 1935 literature, is dated July and was issued in September, 1935. The object of each volume is to cover the literature published in a single year, but in practice many papers have remained unnoted either owing to inaccessibility or to their not being thought worthy of review in " Helminthological Abstracts." The incorporation of the Bibliography of Helminthology will enable the titles of papers which are not printed with the abstracts in the earlier parts to appear in the

final part for each year. The subscription price for the new publication will remain the same as that for " Helminthological Abstracts," *viz.*, 30*s.* each volume.]

ii. The present Bulletin forms part 8 of the Host Catalogue of the well-known Index Catalogue of Medical and Veterinary Zoology compiled by Stiles and his co-workers, and deals with the literature relating to parasites reported for carnivora. It is based on the combined catalogue of the Divisions of Zoology of the Bureau of Animal Industry and of the National Institute of Health (formerly Hygienic Laboratory) at Washington, D.C. As a working reference index it will be of great assistance to parasitologists. *R. L. S.*

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